Taconite Worker Exposures and Associations with Ischemic Heart Disease and Chronic Obstructive Pulmonary Disease Mortality

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE

UNIVERSITY OF MINNESOTA BY

Ashley May Hernandez, MSPH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Bruce H. Alexander, Ph.D., Advisor

Jeffrey H. Mandel, M.D., MPH, Co-advisor

August 2023

Acknowledgements

Everyone has a childhood dream, and mine started with the movie Outbreak – I wanted to become an epidemiologist - but I didn't know quite how to get there. After teaching for a few years after my Bachelor's, I was visiting one of my best friends, Laura Ableman, and she helped me find an epidemiology program in San Antonio, Texas. Little did I know that visit would begin an almost 10-year journey that took my family and me cross country all the way to Minnesota.

Since starting my master's I've had a number of people who have helped me gain confidence in myself and have helped me push myself harder and further than I ever thought possible. My mom has always been there for me no matter what – she's believed in me every step of the way and has always reminded me even at my lowest points that I was capable of anything I set my mind to. My husband Robert left a job he loved and a community that supported him in San Antonio to ensure that I could pursue my dream and my education, and he made sure that I stayed focused and on track even when I thought it might not be possible. He has been an unwavering support and without my mom and my husband, I would not have been able to persevere – especially through the last three years of my PhD that have been some of the most challenging moments of my life thus far.

I also want to thank all of my friends who have supported me along the way. My friend Laura Ableman for helping to unknowingly lead me down this path, and my fellow students who became lifelong friends – Catherine Babcanec, Christina Rosebush, Aubrey Hubbard, Shannon Sullivan, Yang Liu, and Gabriela Bustamante. They are all incredible people who have helped guide me, listened to me vent, helped me grow as an epidemiologist, and have always been there to boost me up whenever I've felt like it's all a bit much. For myself, I truly could not have done this alone, and they have been and continue to be the most wonderful group of people I've had the privilege to know.

I have also had the luck and good fortune to be surrounded by incredible co-workers who modeled for me what a supportive and strong workplace looked like and demonstrated the work that could be accomplished with an incredibly driven and collaborative team. Thank you to Debb Grove and Allison Iwan in Environmental Health Sciences. A huge thank you to Nancy Pengra who abstracted literally thousands of work history records and provided me with a wealth of knowledge related to this taconite cohort – this quite literally would not have been possible without her. And thank you to Carrie Henning-Smith, Megan Lahr, Katy Kozhimannil, Mariana Tuttle, and Julia Interrante – everyone at the University of Minnesota Rural Health Research Center truly inspired me and they are such a considerate and lovely group of people who showed me the amazing work that can be done when you're in a work environment that is inclusive and enjoyable for everyone.

I also owe a huge thank you to my advisor, Bruce Alexander, and my co-advisor, Jeff Mandel, if anyone else had guided me over the past few years I'm uncertain I would have been able to complete this journey. They have both been incredibly understanding and shown me grace when I needed it most and I'm forever thankful and grateful for their support throughout this entire process.

And lastly, my daughter Maddux – she's been an absolute delight and has helped center me when I wondered "Why am I still doing this?". She has taught me so much and brought so much to my life and the lives of her family. When she struggles with a problem, she never gives up, and she doesn't let setbacks stop her from moving forward. She also finds joy and laughter in absolutely everything she does. Her tenacity, grit, and absolute joy helped me focus and led to the completion of this degree.

Dedication

To Robert, Maddux, and my Mom – my support, my joy, and my love.

I'm forever grateful.

Abstract

Background: Taconite mining (i.e., iron mining) began in the late 1800s along the Mesabi range in Minnesota and currently produces the largest amount of iron ore within the United States. Taconite mining and processing results in potential exposures to respirable dust and silica. Previous population and occupational studies have demonstrated potential associations between respirable dust and silica with chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD). Additionally, a previous mortality study among Minnesota taconite workers indicated that IHD mortality was elevated. Although COPD was not elevated in the previous mortality study, IHD and COPD often occur as comorbidities. However, using only the underlying cause of death on a death certificate may result in an under-estimation of the COPD mortality burden particularly in the presence of co-morbidities such as IHD.

Objective: The overall objective of this research is to evaluate the impact of occupational exposures in taconite mining (i.e., employment duration, respirable dust, and respirable silica) on IHD and COPD mortality among a cohort of taconite miners in Minnesota. Specifically, to determine whether the underlying causes of death due to both COPD and IHD were under-or over-estimated, respectively,
this dissertation investigated IHD and COPD mortality among taconite workers using a multiple cause of death analysis. Further, given the potential relationship between employment duration, respirable dust and respirable silica with IHD and COPD,
this dissertation also explored the association between employment duration, respirable dust, and respirable silica with IHD and COPD, respectively, among a cohort of taconite miners.

Specific Aim 1

<u>Aim</u>**:** To determine whether underlying causes of death due to COPD and IHD were under- or over-estimated, respectively, the current study investigated IHD and COPD mortality among taconite workers using a multiple cause of death analysis.

Methods: The referent population was constructed using Minnesota population data from U.S. Census Bureau and mortality data from the Minnesota Department of Health for 1970-2010. Underlying and contributing causes of death were classified using ICD 7-10 codes based on the year of death for each individual. Taconite workers were included in the study if they were part of the Mineral Resource Health Assessment Program and had updated information in 2008 (N=30,779). Standardized mortality ratios (SMRs) were calculated comparing the observed number of deaths among taconite workers to the number of deaths expected in this population based on Minnesota reference rates (using underlying and contributing causes of death due to IHD or COPD).

Results**:** Among deceased taconite workers, 2,127 had IHD listed as the underlying cause of death and an additional 560 workers had IHD listed as a contributing cause of death. A total of 361 workers had COPD listed as the underlying cause of death and an additional 490 had COPD listed as a contributing cause of death. The SMRs for the underlying cause of death were 1.04 (95% CI = 1.00, 1.09) for IHD and 0.85 (95% CI = 0.76, 0.94) for COPD. For an underlying or contributing cause of death due to IHD, the SMR was 1.01 (95% CI = 0.98, 1.05) whereas for COPD the SMR was 0.90 (95% CI = 0.84, 0.97).

Specific Aim 2

Aim**:** To investigate the potential occupational association among a cohort of Minnesota taconite miners between employment duration, respirable dust, and respirable silica with IHD mortality. A secondary analysis was also conducted to determine the impact of potential misclassification of IHD and extended the outcome to include contributing causes of death due to IHD with COPD listed as a primary cause of death.

Methods**:** A nested case-control study within a cohort of 31,067 taconite workers was conducted. Cases were identified based on the vital status of each of the workers through 2010. Cases were selected based on an underlying cause of death of IHD (N=2185) or an underlying cause of death due to IHD *and* a contributing cause of death due to IHD with COPD as the underlying cause of death (N=2217). Two controls were randomly selected via incidence density sampling and caliper matched on birth year (+/- 2 years) and sex. Conditional logistic regression was used to estimate the risk of IHD associated with employment duration (by department, industry, and production department), respirable dust (continuously and by quartiles), and respirable silica (continuously and by quartiles) among taconite miners.

***Results*:** Among underlying cases of IHD, most were employed in taconite on average 11.9 years (SD=10.0) whereas controls were employed on average 12.2 years (SD=10.4). No associations with IHD mortality were identified for employment duration by department, industry, or production departments. Additionally, no association was found between respirable dust (HR=0.99; 95%CI=0.97, 1.02) or respirable silica (HR=1.02; 95%CI=0.84, 1.24) with IHD as an underlying cause of death. Results that included contributing causes of death due to IHD with COPD listed as a primary cause of death were essentially unchanged from those with IHD as an underlying cause of death only.

Specific Aim 3

Aim: To investigate the potential occupational association among a cohort of Minnesota taconite miners between employment duration, respirable dust, and respirable silica with COPD mortality. A secondary analysis was also conducted to determine the impact of potential misclassification of COPD and extended the outcome to include contributing causes of death due to COPD with IHD listed as a primary cause of death.

Methods: A nested case-control study within a cohort of 31,067 taconite workers was conducted. Cases were identified based on the vital status of each of the workers through 2010. Cases were selected based on an underlying cause of death of COPD (N=363) or an underlying cause of death due to COPD and a contributing cause of death due to COPD with IHD as the underlying cause of death (N=499). Two controls were randomly selected via incidence density sampling and caliper matched on birth year (+/- 2 years) and sex. Conditional logistic regression was used to estimate the risk of COPD associated with employment duration (by department, industry, and production

department), respirable dust (continuously and by quartiles), and respirable silica (continuously and by quartiles) among taconite miners.

Results: Among underlying cases of COPD, most were employed in taconite on average 11.5 years (SD=10.3) whereas controls were employed on average 12.0 years (SD=10.7). No associations with COPD mortality were identified for employment duration by department or industry. An association was found by production departments for individuals with unknown work history and laborers (HR=1.04; 95%CI=1.01, 1.07); however, the association was no longer significant when contributing causes of death due to COPD were included (HR=1.01; 95%CI=0.98, 1.03). No association was found between respirable dust (HR=0.98; 95%CI=0.93, 1.04) or respirable silica (HR=0.82; 95%CI=0.51, 1.31) with COPD as an underlying cause of death. Results that included contributing causes of death due to COPD with IHD listed as a primary cause of death were essentially unchanged from those with COPD as an underlying cause of death only.

Overall Conclusion: The results of this study indicate that occupational factors are unlikely to lead to increased IHD or COPD mortality. In Specific Aim 1, no evidence was found that suggested that the inclusion of contributing causes altered the direction of previously reported associations for IHD or COPD among taconite workers as compared to the general Minnesota population. That is, IHD and COPD mortality remained in the same direction with similar magnitudes as a previous study among the same cohort suggesting that the inclusion of contributing causes did not impact the findings. For Specific Aims 2 and 3, the current study did not identify associations between IHD or COPD mortality and employment duration or respirable dust or silica exposures within taconite mining suggesting that occupational factors are unlikely to lead to increased IHD or COPD mortality.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

COPD – Chronic Obstructive Pulmonary Disease

IHD – Ischemic Heart Disease

HR – Hazard Ratio

PM – Particulate Matter

CI – Confidence Interval

Preface

The organization of this dissertation includes an initial introductory chapter, three individual manuscripts written as chapters, and a concluding chapter. The three individual manuscripts are in preparation for peer-review and as a result, there will be some redundancy in material between each of these chapters.

Chapter 1: Introduction

Background and Significance

Taconite mining (i.e., iron mining) along the Mesabi range in Minnesota produces the largest amount of iron ore and taconite within the United States (1). Mining along the Mesabi range began in the early 1900s; however, the original ore that was mined along the range was hematite – a rich iron ore that required little processing (2). As hematite ore became depleted due to high demands for iron ore during the World War II era, taconite ore began to be processed (2). Taconite is a lower grade iron ore which requires more processing than hematite and became the predominant iron ore source in the latter half of the 20th century (2). Taconite mining involves blasting rock from open pits and then crushing and processing the rock to extract iron ore (2, 3). As a result, taconite processing exposes workers to more dust, debris, and other potential exposures than the processing of hematite, resulting in potential excess exposures to respirable dust and silica (3).Concerns about health effects due to occupational exposures as a result of taconite mining have led to studies of taconite miners focused on mesothelioma and other health conditions as well as various exposures including respirable dust and silica (2-12).

Associations between $PM_{2.5}$ and Respirable Dust with IHD and COPD

Respirable dust includes dust particles that are less than or equal to 4 micrometers in aerodynamic diameter (13). Respirable dust includes respirable silica and particulates such as fine particulate matter ($PM_{2.5}$) that have been associated with cardiovascular disease and mortality (14-17). Environmental factors such as $PM_{2.5}$ have been shown to initiate systemic inflammation and oxidative stress in murine models and population-based epidemiologic studies (18-20). Increased exposure to $PM_{2.5}$ increases levels of cytokines and other inflammatory proteins initiating a cascade effect that leads to increased pulmonary and systemic inflammation, which have been identified as precursors to IHD and COPD (18, 20-23). Further, Kaufmann *et al.* determined increases in $PM_{2.5}$ led to subsequent increases in coronary calcium, a precursor to IHD, adding to the biological plausibility of an association between $PM_{2.5}$ and IHD (24). $PM_{2.5}$ has also been found to alter pulmonary vasculature leading to the development of COPD (18-20). Additionally, previous work conducted by Huynh *et al.* within taconite mining found that $PM_{2.5}$ and respirable dust exposures within the mines were highly correlated (25). Occupational exposure to respirable dust has been associated with ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) (17, 26). Further, respirable dust exposures in occupational settings are likely much greater than environmental exposures.

Previous Taconite Exposure Studies

Previous taconite studies have evaluated exposures and health outcomes among this cohort of taconite workers (3-6, 9, 12, 25). Exposures of concern that have previously been evaluated include elongate mineral particles (EMPs), respirable dust, and respirable silica (3, 11, 12, 27). For the current study, previously modeled respirable dust and respirable silica measurements were used (12). Using a combination of historical and more recently (i.e., 2010) collected exposure measurements, a total of 19,391 respirable dust measurements and 9,127 respirable silica measurements were used to model exposure and create a job-exposure matrix (JEM) (12). The respirable dust measurements were modeled by mine and previously established departments (i.e., mining, crushing, concentrating, pelletizing, shop (mobile), shop (stationary), office/control room, and janitor) by year beginning in 1955 until 2010 (12). The estimates for respirable dust were highest among the crushing department (yearly average among all 7 mines in 1955 = 2.03 mg/m^3; and in 2010 = 1.44 mg/m^3) and lowest in the office/control room department (yearly average among all 7 mines in 1955 = 0.00 mg/m^3; and in 2010 = 0.13 mg/m^3) with some respirable dust exposures that were greater than the Mine Safety and Health Administration (MSHA) 8-hour TWA of 1.5 mg/m^3 (12). Further, respirable silica was also modeled and based on the assumption that the percentage of silica content in respirable dust and taconite ore remained unchanged over time. For respirable silica, the highest concentrations occurred in crushing (yearly average among all 7 mines in 1955 = 0.27 mg/m^3; and in 2010 = 0.19

mg/m^3) and shop (mobile) (yearly average among all 7 mines in 1955 = 0.14 mg/m^3; and in 2010 = 0.08 mg/m^3) with some respirable silica measurements exceeding the MSHA 8-h TWA of 0.1 mg/ m^3. Using these data, the current study established cumulative estimates of exposure for each taconite mining industry worker.

Previous Taconite Mortality Study

In a previous mortality study conducted by Allen *et al.*, the investigators found that IHD mortality rates in this population were elevated as compared to the Minnesota population (SMR=1.11; 95%CI=1.07, 1.16) (6). While Allen *et al.* did not find an increase in COPD mortality (SMR=0.98; 95%CI=0.88, 1.09), IHD and COPD often occur as comorbidities and, particularly in the presence of cardiovascular disease, underreporting of COPD on the death certificate often occurs (28-33). Given that underreporting on the death certificate occurs and COPD is often not listed as the primary cause of death when it does occur, a multiple cause of death analysis was used for the current study. Multiple cause of death analysis allows for the extension of the cause of death beyond the primary cause of death to contributing causes of death as well (33, 34). A multiple cause of death analysis was not only used in the current study to calculate SMRs by extending the definition of the cause of death beyond the primary cause to contributing causes, but also as a sensitivity analysis for the analyses that investigated the associations between taconite exposures and IHD and COPD, respectively.

Objective

The overall objective of this research is to evaluate the impact of occupational exposures in taconite mining (i.e., employment duration, respirable dust, and respirable silica) on IHD and COPD mortality among a cohort of taconite miners in Minnesota.

Specific Aims

The overall objective of this research is accomplished in three manuscripts that have the following specific aims:

<u>Specific Aim 1 (Chapter 2):</u>

To determine whether underlying causes of death due to COPD and IHD were under- or over-estimated, respectively, the current study investigated IHD and COPD mortality among taconite workers using a multiple cause of death analysis.

<u>Specific Aim 2 (Chapter 3):</u>

To investigate the potential occupational association among a cohort of Minnesota taconite miners between employment duration, respirable dust, and respirable silica with IHD mortality. A secondary analysis was also conducted to determine the impact of potential misclassification of IHD and extended the outcome to include contributing causes of death due to IHD with COPD listed as a primary cause of death.

<u>Specific Aim 3 (Chapter 4):</u>

To investigate the potential occupational association among a cohort of Minnesota taconite miners between employment duration, respirable dust, and respirable silica with COPD mortality. A secondary analysis was also conducted to determine the impact of potential misclassification of COPD and extended the outcome to include contributing causes of death due to COPD with IHD listed as a primary cause of death.

Chapter 2: Multiple Cause of Death Analysis among Minnesota Taconite Mining Industry Workers

Introduction

In a previous study of taconite workers that exclusively used the underlying cause of death as reported in death certificates, Allen *et al.* found an elevation in IHD mortality as compared to the general Minnesota population (6). However, COPD mortality was not elevated as compared to this referent population, and it is possible that these findings related to COPD could be due to disease misclassification or misdiagnosis of the cause of death on the death certificate (6, 33). Additionally, smoking is a risk factor for both IHD and COPD, and it is important to note that Allen *et al.* were not able to adjust for smoking (6).

In terms of causes of death, death certificates contain both underlying and contributing (or intervening causes of death. The underlying cause of death is defined as “the disease or injury that initiated the train of morbid events resulting in death…” whereas the contributing or intervening causes are defined as “other conditions that contribute to death and are a result of the underlying cause” (35). For mortality statistics, the focus is generally on the underlying cause of death under the assumption that acting upon the underlying cause is best-suited to prevention of death. However, relying solely on the underlying cause of death may result in misclassification, particularly for chronic diseases that may co-occur (33).

Mortality data for chronic disease outcomes, such as COPD, is not always reliable because an individual may have multiple chronic diseases (e.g., COPD and heart disease) at the same time. In fact, COPD is often not recorded as an underlying cause of death on death certificates and even among those with confirmed COPD, studies have found that COPD is often not recorded on the death certificate at all (29, 30, 32). As a result, distinguishing the underlying cause of death for an individual with multiple comorbidities poses a challenge. Additionally, contributing causes of death are often not recorded on the mortality record. Further, if they are recorded, these contributing causes of death are often ignored (33). For instance, consider an individual with COPD and heart disease. The individual's ultimate cause of death may be listed on the death certificate as ischemic heart disease. Although the death certificate would list ischemic heart disease as the underlying cause of death, COPD would be listed only as a contributing cause of death. If only the underlying cause of death is recorded or considered, the individual's co-occurring cause of death, COPD, would be missed.

For example, in a study by Mannino *et al.*, among those with obstructive lung disease mentioned as either an underlying or contributing cause on the death certificate, only 43.3% had obstructive lung disease listed as the underlying cause of death (34). These findings suggest that obstructive lung disease was underestimated when the underlying cause of death was considered alone. Additionally, the Mannino *et al.* study highlights the importance of utilizing contributing causes of death when exploring diseases such as COPD that may be important factors in the cause of death, but not listed as the underlying cause (34). However, relying solely on the underlying cause of death may lead to an under- or over-estimation of the mortality burden, particularly in the case of COPD and heart diseases, respectively (33).

Given that reliance on the underlying cause of death alone may under- or over-estimate the mortality burden of COPD and IHD, respectively, the current study utilized multiple cause of death analysis. Multiple cause of death analysis extends the definition of the cause of death to include not only the underlying cause of death, but also the subsequent causes of death for outcomes that are often misclassified such as COPD. The current study will investigate IHD and COPD mortality among taconite workers using a multiple cause of death analysis.

Methods

Taconite Workers Data Collection

In the 1980s, concerns arose about taconite miners' health and potential health effects that may be due to the occupational exposures they experience. As a result, the Mineral Resources Health Assessment Program (MRHAP), a collaboration between the Iron Range Resources and Rehabilitation Board and the University of Minnesota's School of Public Health, was formed. In 1983, employee records for 68,737 workers were collected from seven existing mines including US Steel Corporation, Hanna Mining Company, Pickands-Mather and Company, Reserve Mining Company, Eveleth Taconite Company, Inland Steel Company, and Jones and Laughlin Corporation. Social Security Administration (SSA) records were used to determine whether workers had died or were still living through 2010 (6). Based on SSA records, if a worker had died, mortality data was obtained via the National Death Index, Minnesota Department of Health, or other state departments (6).

In 2008, the health assessment of these taconite workers was updated as part of the University of Minnesota's Taconite Workers Health Study (TWHS). Given workers within this occupational cohort included both hematite and taconite workers, and the focus of the current study is taconite workers, the following exclusions to the original MRHAP cohort were made to ensure mainly taconite workers' experience was captured. Since taconite mining began mainly in the 1950s, only workers who were born in 1920 or later were included in the current study (n=46,170). Additionally, we excluded individuals who only had an application on file and no additional work history (n=477), individuals for whom vital status could not be ascertained (n=679), and individuals who were likely not employed (e.g., those younger than 14 at the time of employment) (n=539). Further, since reference population data for the current study were not available prior to 1970, an additional 513 workers were excluded from the study. To ensure the current study focused on workers with more stable employment in the industry (i.e., not summer workers or temporary workers), workers who worked less than 1 year were also excluded (n=13,179). Of the remaining workers, four workers had an unknown sex and were also excluded from the study. In total, 30,779 workers were included in the current analysis (**Figure 1**).

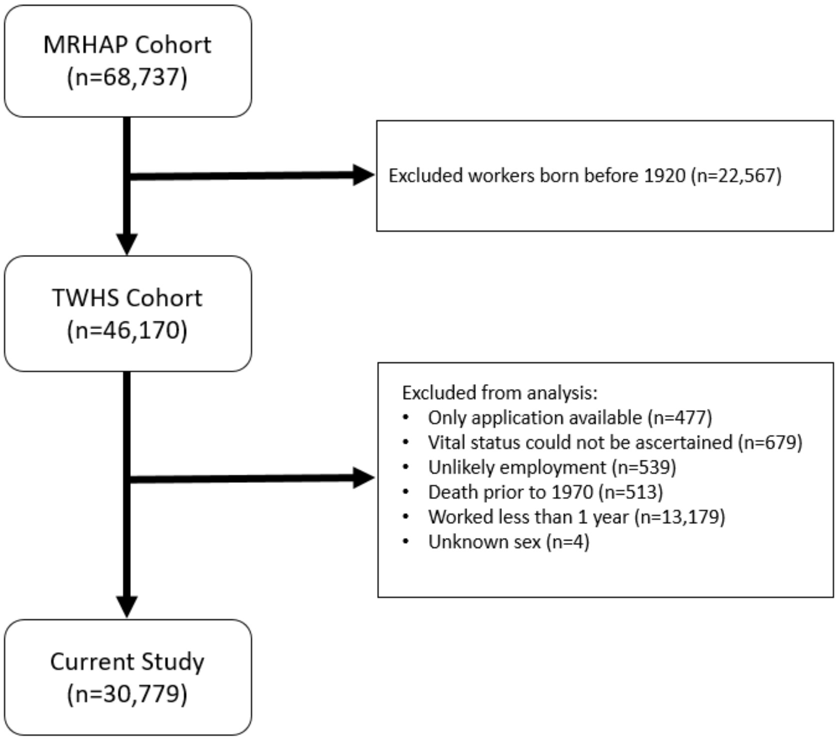

Figure 1. Study Exclusion Criteria

Referent Population Data Collection

The general Minnesota population was used as the reference population. Minnesota population data was collected from the U.S. Census Bureau for the years 1970-2010 (36-39). For the years 1980-2000, data was available at the county-level within the state; as a result, these data were aggregated to create state-level estimates by sex, race, and age group.

Mortality data for the reference population was collected from Minnesota Department of Health for the years 1960-2010 (40). However, since population data was only available from 1970 onward, the mortality data for the general Minnesota population was only used for 1970-2010. Mortality and population data was stratified by age, sex, race and year. All underlying and contributing causes of death for the Minnesota population were provided for this time period (1970-2010) (40). To determine which deaths were due to ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD), respectively, NIOSH-119 designations for IHD and COPD were used based on ICD-7, ICD-8, ICD-9, & ICD-10 codes by the year of death for each individual (41). Additionally, no race data was available on taconite workers within the current study and were assumed to be predominately White, as a result all other race categories in the Minnesota population and mortality data were not considered for the current study. Lastly, information on job status was not available for the entire study cohort at the time of this analysis.

Data Analysis

To determine the standardized mortality ratios (SMRs), both underlying cause of death due to IHD or COPD and contributing causes of death due to IHD or COPD were used. Contributing causes of death included underlying causes of death in addition to any cause of death mentioned in the contributing causes that was related to IHD or COPD, respectively.

To calculate the SMR the observed number of deaths among taconite workers was compared to the number of deaths expected in the taconite worker population based on Minnesota population reference rates. Within each strata of 5-year age, calendar period, sex, and race, the number of taconite workers was multiplied by the Minnesota population reference rates and these products were then summed to determine the overall expected number of deaths. A Poisson process was used to calculate exact 95% confidence intervals for each SMR.

R and Stata were used for all statistical analysis.

Results

Of the 30,779 taconite workers included in the current study, the average year of birth was 1940 (SD = 12.0) and the majority were male (92.9%) (**Table 1**). Most workers were hired between the ages of 20 and 29 (37.5%) and most of the hiring within this cohort took place between 1970 and 1979 (33.5%) (**Table 1**). Most workers within the taconite cohort were still alive as of 2010 when vital status data was collected (n=20,810; 67.6%) (**Table 1**).

A total of 2,127 workers died due to an underlying cause of death of IHD, and an additional 560 had IHD listed as a contributing cause of death (**Table 1**). Three hundred and sixty-one workers died due to an underlying cause of death of COPD, and an additional 490 workers died due to an underlying or contributing cause of death of COPD (**Table 1**).

Compared to the overall cohort of taconite workers (n=30,779), those who died due to IHD or COPD were older (with the average year of birth of 1929 and 1928, respectively, versus 1940 for the entire cohort) (**Table 1**). Additionally, of those who died due to IHD as an underlying cause of death, 98.0% were men, whereas for those with an underlying cause of death of COPD, 95.6% were men (**Table 1**). For underlying or contributing causes of death due to IHD, 98.1% were men, and for COPD, 96.2% were men (**Table 1**).

Table 1. Characteristics of Taconite Workers with a Date of Death Between 1970 and 2010 by Underlying and Contributing Causes of Death Due to IHD and COPD

	Underlying Cause of Death				**Underlying + Contributing Cause of Death**				**Total**	
	IHD (N=2127)		COPD (N=361)		IHD (N=2687)		COPD (N=851)		(N=30779)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Average Birth Year	1929	8.14	1928	6.33	1929	7.98	1928	6.52	1940	11.97
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex										
Male	2,085	98.0	345	95.6	2,637	98.1	819	96.2	28,585	92.9
Female	42	2.0	16	4.4	50	1.9	32	3.8	2,194	7.1
Age at Hire										
<20	614	28.9	92	25.5	760	28.3	213	25	11,544	37.5
20-29	1,129	53.1	185	51.2	1,438	53.5	445	52.3	15,808	51.4
30-39	302	14.2	60	16.6	391	14.5	152	17.9	2,810	9.1
40+	82	3.8	24	6.7	98	3.7	41	4.8	617	2.0
Decade of Hire										
<1950	763	35.9	121	33.5	968	36	300	35.3	4,454	14.5
1950-1959	934	43.9	175	48.5	1,183	44	407	47.8	8,920	29
1960-1969	270	12.7	38	10.5	345	12.8	92	10.8	6,867	22.3
1970-1979	157	7.4	27	7.5	187	7	50	5.9	10,329	33.5
>1980	3	0.1	0	0	4	0.2	2	0.2	209	0.7
Vital Status										
Alive	-	-	-	-	-	-	-	-	20,810	67.6
Dead	2,127	100	361	100	2,687	100	851	100	8,689	28.2
Presumed Alive	-	-	-	-	-	-	-	-	1,157	3.8
Presumed Dead	-	-	-	-	-	-	-	-	123	0.4

IHD=Ischemic Heart Disease; COPD=Chronic Obstructive Pulmonary Disease

The SMRs for the underlying cause of death were 1.04 (95% CI = 1.00, 1.09) for IHD and 0.85 (95% CI = 0.76, 0.94) for COPD (**Table 2**). For an underlying or contributing cause of death due to IHD, the SMR was 1.01 (95% CI = 0.98, 1.05) whereas for COPD the SMR was 0.90 (95% CI = 0.84, 0.97) (**Table 3**).

Table 2. Standardized Mortality Ratios (SMRs) for Underlying Causes of Death due to Ischemic Heart Disease (IHD) and Chronic Obstructive Pulmonary Disease (COPD)

Underlying Cause	Observed	Expected[a]	SMR	95% CI
IHD	2127	2044.1	1.04	(1.00, 1.09)
COPD	361	426.5	0.85	(0.76, 0.94)

[a] Based on Minnesota population data from U.S. Census Bureau and mortality data from the Minnesota Department of Health for 1970-2010

Table 3. Standardized Mortality Ratios (SMRs) for Underlying and Contributing Causes of Death due to Ischemic Heart Disease (IHD) and Chronic Obstructive Pulmonary Disease (COPD)

Underlying & Contributing Cause	Observed	Expected[a]	SMR	95% CI
IHD	2687	2650.1	1.01	(0.98, 1.05)
COPD	851	942.3	0.90	(0.84, 0.97)

[a] Based on Minnesota population data from U.S. Census Bureau and mortality data from the Minnesota Department of Health for 1970-2010

Discussion

Utilizing multiple cause of death analysis provides an opportunity to determine whether there is potential misclassification of cause of death that may have occurred, particularly for chronic conditions for which there may be other comorbidities at the time of death (33). In the current study, including the contributing causes of death for COPD did result in a slightly higher SMR indicating that it is possible that some misclassification of disease for may be possible. Similarly, when contributing causes were taken into account for IHD, the SMR was slightly attenuated which may also indicate some misclassification for the underlying cause was possible. This indicates it may be possible that COPD was underestimated and IHD was overestimated as suggested by other studies investigating multiple cause of death analysis (33, 34).

Despite the potential for misclassification of disease, the findings of the current study do not indicate that IHD is increased among taconite workers as compared to the general Minnesota population. These results are dissimilar from the findings of a study conducted by Allen *et al.*, in which IHD was found to be increased among taconite workers as compared to the general Minnesota population (6). However, there are notable differences between the Allen *et al.* study and the current study.

In Allen *et al.*, the taconite workers and Minnesota reference population were considered from 1960 onward; the current study only considers 1970 onward (6). It is possible that additional deaths due to IHD between 1960 and 1970 may have contributed in part to the increased SMR found in the Allen *et al.* study, however, this likely played a small role in the slight differences found in the current study (6). However, it is more likely that the differences identified between the Allen *et al.* study and the current study are due to the differences in the reference rates used (6). The Allen *et al.* study utilized the Life Table Analysis System (LTAS) to calculate SMRs, and at the time of the study, the National Center for Health Statistics (NCHS) provided state-based rates to LTAS (6, 42). For the current study, LTAS could not be used because the agreement with NCHS changed and state-based rates were no longer available (42). As a result, there may be slight differences between the reference rates used in this study compared to the Allen *et al.* study which may contribute to the differences in SMRs found for the underlying cause of death of IHD between the current study and the Allen *et al.* study. However, despite these differences, the direction of the SMRs remained the same for both IHD and COPD and are comparable between the Allen *et al.* study and the current study.

Similar to the Allen *et al.* study, the current study suggests that deaths due to COPD are not elevated among taconite workers as compared to the general Minnesota population (6). In fact, the current study indicates that deaths due to COPD may even be reduced among the taconite population as compared to the general Minnesota population. However, it is possible that this perceived reduction in deaths due to COPD may be due to the older age distribution of the current study population. That is, it is possible that those who were born in the late 1920s may have died due to other causes more prevalent at their time of death than COPD or IHD (i.e., competing causes of death) which would lead to reduced estimates for both COPD and IHD, respectively, that would otherwise be greater in magnitude had the cohort been younger (i.e., been born on average in the 1950s for example).

There are limitations to the current study. There are lifestyle and behavioral factors that have been associated with deaths due to IHD and COPD. These factors include smoking, blood pressure, and lipid abnormalities. Given that no information was available for these particular factors and that there is uncertainty regarding the distribution of these factors among cases and controls, it is not possible to determine how accounting for these factors could impact the current findings of the study. That is, accounting for these factors may lead to an increase or reduction in effect, and the specific impact adjustment for these factors may have is unknown.

The use of death certificates to define cause of death may also under- or over-estimate mortality due to IHD or COPD. Specifically in relation to COPD, previous studies have found that COPD is often underreported or not reported on the death certificate all together (29, 30, 32). Additionally, there may also be differences between ICD definitions of disease that lead to differences in the estimates of disease burden due to COPD or IHD. For example, Yoon and Chow determined that the odds for ICD-10 to predict a COPD diagnosis increased between ICD-9 and ICD-10 (OR=1.16; $p<0.001$) whereas those for ischemic heart disease decreased (OR=0.69; $p<0.001$) (43). Although Yoon and Chow investigated prevalent diagnosis of COPD and IHD and not mortality, their study demonstrates the differences that may occur between ICD revisions. While the current study cannot address lack of reporting of COPD or IHD as a cause of death on the death certificate, the study does account for the inclusion of contributing causes of death due to COPD to address potential under-estimates of the burden of COPD mortality.

It is also possible that the findings of the current study are further influenced by the healthy worker effect, particularly since the causes of death of interest are chronic diseases (IHD and COPD) (44). For those with chronic diseases, such as COPD, they may immediately be selected out of the working population, particularly for industries for which the exposures could potentially exacerbate those conditions. As a result, the workers that are selected into the working taconite population may be healthier than those in the general population. For the current study, the healthy worker effect could, in part, explain the reduced mortality due to COPD among taconite workers as compared to the general Minnesota population. Further, the healthy worker effect may also be affected by unhealthy workers being selected out of the workforce. However, given the length of follow up for the current taconite population, which begins at the worker's start date and ends at the ascertainment of vital status, this is unlikely to have an effect. Lastly, duration of employment within the taconite industry could theoretically play a role in mortality due to IHD and COPD, due to longer exposure times. However, Allen *et al.* did not find that employment duration was associated with increased death due to IHD indicating that mortality due to IHD may not be a function of time spent within the industry, but rather due to specific exposures (or other risk factors). Further analysis investigating particular exposures within the taconite industry and stratifying by employment time in production versus nonproduction positions within taconite would help elucidate whether specific production activities within taconite result in increased mortality.

Conclusion

The current study did not find evidence of elevated mortality due to IHD or COPD among taconite workers as compared to the general Minnesota population based on use of underlying cause of death alone, nor based on the combination of underlying and contributing causes of death. While the utilization of multiple cause of death analysis did reveal that there is potential misclassification of death due to IHD and COPD among taconite workers, the direction of the effect were similar for both the underlying cause of death analysis and the analysis combining underlying and contributing causes of death. These results suggest that Minnesota's taconite workers are not at higher risk of mortality from IHD or COPD compared to the general population of the state. Further, no evidence was found that suggested that the inclusion of contributing causes of death altered the direction of previously reported associations among taconite workers as compared to the general Minnesota population.

Chapter 3: Ischemic Heart Disease Mortality among Minnesota Taconite Mining Industry Workers

Introduction

Heart disease is the leading cause of death in the United States. Most deaths due to heart disease are a result of ischemic heart disease (IHD) (23, 45, 46). IHD typically occurs when the heart does not receive enough blood and oxygen due to the narrowing of arteries leading to the heart, which is most commonly caused by atherosclerosis, a buildup of plaque in the arterial wall; however IHD may also result from cardiomyopathy, toxins, or valvular heart disease (23, 46, 47). Risk factors for atherosclerosis include non-modifiable factors such as age, race and ethnicity, and genetics, but also include modifiable or controllable risk factors such as abnormal lipids, smoking, physical inactivity, hypertension, and insulin resistance (a precursor to type II diabetes) (23, 46). Further, those with IHD often have comorbidities including COPD, which can lead to additional adverse health outcomes than with IHD alone (48).

In Minnesota, iron ore mining has been an integral part of the state's economy since the early 20th century (49). Following the depletion of the reserves of hematite iron ore, the mining of taconite, a lower grade iron ore which requires processing for use in steel production, became the predominant iron ore source in the latter half of the 20th century (2). Taconite mining involves blasting rock from open pits and then crushing and processing the rock to extract iron ore (2, 3). Concerns about health effects of occupational exposures have led to studies of taconite miners focused on mesothelioma and other health conditions (2, 4-10). In a previous mortality study conducted by Allen *et al.*, the investigators found that IHD mortality rates in this population were elevated as compared to the Minnesota population (6).

Taconite mining and processing can result in several potentially harmful exposures, including elongate mineral particles (EMPs), respirable silica, and respirable dust (3, 11, 25). While there have been few occupational studies investigating the role respirable dust (aerodynamic diameter ≤4μm) plays in adverse IHD outcomes, there have been a number of population-based studies that have found a relationship between increases in $PM_{2.5}$ (aerodynamic diameter ≤2.5μm) and adverse cardiovascular outcomes (14, 15, 20, 50, 51).

Environmental factors such as $PM_{2.5}$ have been shown to initiate systemic inflammation and oxidative stress in murine models and population-based epidemiologic studies (18-20). Increased exposure to $PM_{2.5}$ increases levels of cytokines and other inflammatory proteins initiating a cascade effect that leads to increased pulmonary and systemic inflammation, which have been identified as precursors to IHD (18, 20, 23). Further, Kaufmann *et al.* determined increases in $PM_{2.5}$ led to subsequent increases in coronary calcification, which can be a precursor to IHD, adding to the biological plausibility of an association between $PM_{2.5}$ and IHD (24). Although $PM_{2.5}$ and respirable dust are differently sized particles of different sizes, previous work conducted by Huynh *et al.* within taconite mining found that $PM_{2.5}$ and respirable dust exposures within the mines were highly correlated (25). Further, respirable dust includes respirable silica that has also been associated with cardiovascular disease and mortality (16, 17).

To determine whether working in taconite affects IHD mortality, the current study investigated employment duration, respirable silica, and respirable dust exposure on IHD. In addition to the primary objective, an exploration of potential misclassification of IHD as an underlying cause of death was also undertaken, since reliance on ~~solely~~ the underlying cause of death may lead to misclassification when co-morbidities such as COPD are present (33). Because of this concern, a secondary objective was to evaluate the potential misclassification of IHD as an underlying cause of death by identifying contributing causes of IHD mortality where COPD was classified as the underlying cause of death.

Methods

Study Design & Population

We conducted a nested case-control study within a cohort of iron mining workers. In 1983, employee records for 68,737 workers were collected from seven existing taconite mines as part of the Mineral Resources Health Assessment Program (MRHAP), a collaboration between the Iron Range Resources and Rehabilitation Board and the University of Minnesota's School of Public Health, in order to investigate the health effects taconite workers may experience due to occupational exposures. In 2008, the health assessment of these taconite workers was updated as part of the University of Minnesota's Taconite Workers Health Study (TWHS). As part of this update, the vital status of each of the workers was obtained through 2010 by utilizing data from the National Death Index, Social Security Administration, Minnesota Department of Health and state death certificates for individuals who expired outside of Minnesota. International Classification of Disease (ICD) codes that were in effect at the time of death were used.

While the exposures of interest for this study are from taconite mining and processing, this cohort included both hematite and taconite workers. To focus on taconite mining, which began in the 1950s, workers who were born in 1920 or later were included in the current study (N=46,170). Additional exclusions included cohort members whose employment record was limited to an application (N=477), for whom vital status could not be ascertained (N=679), and were likely not employed (e.g., those younger than 14 at the time of employment) (N=539). Further, individuals who died prior to 1960 were also excluded (n=232) since mortality data was not as comprehensive prior to that year. To ensure the current study focused on workers with more stable employment in the industry (i.e., not summer workers or temporary workers), workers who worked less than 1 year were also excluded (n=13,176). In total, cases and controls were selected from 31,067 workers included in the current cohort.

Selection of Cases & Controls

The primary objective was to determine the association between exposures experienced among taconite miners (i.e., employment duration, respirable silica, and respirable dust exposure) and IHD mortality. Given that reliance on the underlying cause of death alone may lead to misclassification when co-morbidities such as COPD are present, a secondary objective was to determine the potential misclassification of IHD as an underlying cause of death by including contributing causes of IHD mortality where COPD was classified as the underlying cause of death (26). As a result, cases were defined in two ways based on how IHD was listed on the death certificate: 1) IHD underlying and 2) IHD underlying/contributing. IHD underlying cases included cases identified as IHD from the underlying cause of death listed on the death certificate. IHD underlying/contributing cases included *all* IHD underlying cases *in addition to* IHD cases identified as contributing causes on the death certificate with COPD as an underlying cause on the death certificate.

As noted above, cases included all decedents with IHD as the underlying cause of death (IHD underlying: N=2185) based on NIOSH-119 designations (**Supplemental Table 1**) (41). A secondary set of IHD cases was identified where COPD was the underlying cause of death and IHD was a contributing cause of death to explore the potential for misclassification of IHD (IHD contributing: N=32; IHD underlying/contributing: N=2217).

For each case, two controls were randomly selected using an incidence density sampling scheme. The controls were selected from risk sets of all cohort members alive at the year of death of the case and matched on birth year (+/- 2 years) and sex.

Work History Abstractions

Work history abstractions for each case and control were completed to gather information for each workers' employment history. These records included information on workers' specific job titles, their start and end dates for each position they held, and the mining company (i.e., mine) for which they worked. Each workers' job title was standardized and then grouped into previously established similar exposure groups (SEGs) (3, 5, 9, 12). If job and department information was not available, the job title was assigned to an "unknown" SEG.

The SEGs were then grouped into specific departments. Additionally, for work histories that did not have job titles, department information was used to map workers to the appropriate department. Hwang *et al.* and Shao *et al.* created job exposure matrices based on 8 departments including: mining, crushing, concentrating, pelletizing, shop mobile, shop station, office/control room, and janitor (3, 12). However, for the current study, janitors had the smallest department in the current study compared to other groups and were assigned to shop(mobile). The current study also included 3 additional departments: ore dressing, laborer, and unknown. Ore dressing is a department that was not used in previous studies, but encompassed work done in both crushing and concentrating. The laborer category included job titles that indicated the worker was in an "assigned labor" position, for example, but did not have a specific department identified in the employment records. The unknown category encompassed job titles that could not be mapped to an SEG and for which the department could not be identified, or the worker only had employment information related to the mine, but no information on the work conducted by the worker (i.e., no job title information was available).

Finally, while most workers worked in taconite, some workers included in the study worked in both hematite and taconite, and some worked in only hematite. Since exposures experienced in hematite were different than those experienced in taconite, a final department, hematite was created to separate hematite work history from taconite work history. If a workers' start date for a particular job title began prior to the start of taconite for that specific mine or if their job title indicated that they worked in hematite (e.g., a job title of "underground"), they were assigned to a hematite department.

Exclusions to cases and controls were made if there was no evidence that an individual worked in hematite or taconite mining. After these exclusions, if cases or controls no longer had at least one match, these workers were also dropped from the study. This led to 2,105 cases and 4,061 controls for the analysis of IHD as an underlying cause of death (i.e., IHD underlying), with only one control per case for 149 cases and two controls per case for the remaining 1,956 cases. For the secondary analysis that included contributing causes of IHD (i.e., IHD underlying/contributing), after these exclusions, there were 2,135 cases and 4,119 controls remaining, with only one control per case for 151 cases and two controls per case for the remaining 1,984 cases.

Employment Duration

To calculate employment duration, the start and end dates for each position held by each worker for each job were used. For a particular job title, if no start or end date was recorded, that particular job was dropped from the analyses. Similarly, if the start and end date were the same for a particular job title, these jobs were also dropped from the analyses. After these exclusions, all workers had a known start date for the first position that they held within the mine. For unknown start dates with an end date, the day after the previous job's end date was imputed as the start date. For known start dates with unknown end dates, the day before a subsequent job's start date was imputed as the end date. For known start dates with unknown end dates that served as the last position held for a worker, the end date was imputed in two ways. For controls with an unknown end date, the vital status date of the case was imputed as the end date. Otherwise, December 31, 1982 was imputed as the end date since employment information was not captured from 1983 onward.

For each worker, cumulative employment duration was calculated by adding the total time (in years) each worker spent within a specific department (i.e., mining, crushing, concentrating, ore dressing, pelletizing, shop mobile, shop stationary, laborer, office/control room, and unknown). Cumulative employment duration was also calculated for those working in hematite. Additionally, a production variable which was the cumulative employment duration (in years) for those working in mining, crushing, concentrating, ore dressing, and pelletizing was also created along with a non-production variable which was the cumulative employment duration (in years) of those working in non-production areas (i.e., shop mobile, shop stationary, office/control room).

Respirable Dust and Respirable Silica Exposure

The mineralogical composition of the rock differs by the location of the mines in the Mesabi Iron Range with mines in the eastern zone having a different geology than those in the western zone, as a result, the exposures experienced due to processing these rocks may differ (3, 11, 52, 53). To characterize respirable dust and silica exposures within the mines, Hwang *et al.* collected personal air samples from active mines in the Mesabi Iron Range including one mine in the eastern zone and five mines in the western zone between 2010 and 2011 (3, 11, 52). Hwang *et al.* selected workers within each SEG at each mine to collect samples using personal air sampling pumps (3). Hwang *et al.* further classified each SEG into a department except for janitors whose exposure profile differed from other departments (3).

Mine specific exposures collected by Hwang *et al.* were used by Shao *et al.*, in addition to historical personal and area samples, to reconstruct respirable dust and silica exposures from 1955 to 2010 (12). The reconstructed respirable dust and silica exposures calculated by Shao *et al.* were then placed into a job exposure matrix by year (1955 to 2010), mine, and department (12).

To estimate the respirable dust and silica exposure experienced by each worker within each department, the information collected from employment duration was combined with the reconstructed exposure data from Shao *et al.* (12). Cumulative respirable dust and silica exposure were estimated by multiplying respirable dust and silica for each year, mine, and department by the respective employment duration identified for each worker by year, mine, and department. The summation of these products was used to determine cumulative exposure for each worker in (mg/m^3)*years for respirable dust and respirable silica, respectively.

To calculate exposures for the “unknown” department, respective mine average estimates for all 8 departments by year were used. For those assigned to the “ore dressing” department, exposures were calculated based on the average exposures within the crushing and concentrating departments combined. Exposures for the laborer category were based on the average of all non-office departments (i.e., mining, crushing, ore dressing, concentrating, pelletizing, shops(stationary), and shops(mobile)). Since the exposure profile of janitors differed from that of other departments, Shao *et al.* grouped them into their own department (12). However, in the current study, janitors were assigned shop(mobile) exposure. In conclusion the following departments were utilized for respirable dust and silica exposure: mining, crushing, concentrating, ore dressing, pelletizing, shop mobile, shop stationary, office/control room, laborer, and unknown.

Further, in some cases, exposure data for a particular mine was not available if the mine was a taconite mine prior to 1955. In these cases, the all mine averages by department from 1955 were used to estimate exposures prior to 1955.

Descriptive Characteristics

Population Characteristics

For 1) the IHD underlying cause of death analysis (IHD underlying) and 2) the IHD underlying or contributing cause of death (IHD underlying/contributing) analysis, characteristics of cases and controls were described by average year of birth, sex (male, female), and the ore type in which each worker worked (hematite only, taconite only, taconite & hematite). The number of cases and controls were also described by decade of birth.

Employment Duration

For IHD underlying and IHD underlying/contributing analyses, employment duration was described by the average number of cumulative years employed in any taconite or hematite industry as well as the average number of cumulative years employed in any department. Employment duration was also presented as the average number of cumulative years employed in production and non-production departments (**Supplemental Table 2**).

Quartiles of total employment duration in taconite and quartiles of total employment duration in production departments were also created based on the distribution of the cases for IHD underlying and IHD underlying/contributing, respectively (**Supplemental Table 3**).

Respirable Dust and Respirable Silica Exposures

Cumulative respirable dust and respirable silica exposures were described by the average cumulative exposure in taconite (in mg/m^3*years). Separate quartiles for cumulative respirable dust and respirable silica exposure were created based on the distribution of the cases for both IHD underlying and IHD underlying/contributing, respectively (**Supplemental Table 3**).

Regression Analyses

Conditional logistic regression was used to estimate the hazard ratios and 95% confidence intervals to characterize the association between employment duration, respirable dust, and respirable silica exposure with IHD mortality. Since controls were sampled using incidence density sampling of the person-time distribution of the cohort, the results of models can be interpreted as hazard ratios.

Models were estimated separately for associations between employment duration, as well as for associations between cumulative exposure for respirable dust and respirable silica with 1) IHD underlying and 2) for IHD underlying/contributing.

Controls were selected based on birth year (+/- 2 years) and sex, limiting the possibility of residual confounding given the close caliper matching for birth year, age, and sex. The independent variables of employment duration and cumulative exposure for respirable dust and respirable silica were included in each model as continuous variables and categorical variables to describe taconite workers' employment duration and cumulative exposure experience.

For employment duration (in years), risk estimates were initially adjusted for number of years spent within each department, including hematite. A separate model was created by utilizing a continuous variable for any employment in taconite (in years) as well as employment in hematite (in years). Lastly, a model accounting for employment duration within production and non-production departments, as well as unknown departments (which included the laborer department) and hematite was also created.

Employment duration was also described and modeled categorically using two models. By using categorical designations of a continuous variable, the effect of potential outliers on the model are reduced and it can assist in determining trends with increasing exposures. One model categorized employment duration into five categories including four categories representing quartiles of cumulative employment duration in taconite and the last category representing employment within hematite only. The second model categorized employment duration into six categories including four categories representing quartiles for production, as well as a category for non-production only (which included unknowns), and hematite only.

Associations between cumulative respirable dust (mg/m^3*years) and respirable silica (mg/m^3*years) with IHD mortality were first accounted for by utilizing a continuous variable for overall cumulative exposure (where hematite exposure was represented as no exposure, i.e., 0 mg/m^3*years) for each exposure, respectively.

Unlike continuous exposure variables, categorical classifications of exposure do not ascribe a particular exposure-response curve to the data. Further, categorization of exposure may provide insight into potential levels of exposure at which there are no observed adverse effects and assist in understanding whether there is an increasing effect with increases in exposure levels. As a result, associations between cumulative respirable dust (mg/m^3*years) and respirable silica (mg/m^3*years) exposures were also described and modeled categorically. The categorical model categorized exposure into five categories including four categories representing quartiles of cumulative respirable dust and cumulative respirable silica, respectively, and the last category represented those who were employed within hematite only (i.e., they had zero respirable dust or respirable silica exposure due to work within the taconite industry).

Results

Characteristics of Cases and Controls

For IHD underlying, cases and controls were predominantly male (cases: n=2,069, 98.3%; controls: n=3,990, 98.3%) (**Table 4**). The distribution of employment by ore type (i.e., hematite only, taconite only, and taconite & hematite) was similar among cases and controls (**Table 4**). The average birth year for cases and controls was 1928 (**Table 4**).

Table 4. Characteristics of Ischemic Heart Disease (IHD) Cases[a] and Controls

	IHD Cases		Controls	
	Mean	**SD**	**Mean**	**SD**
Birthyear	1928	7.87	1928	7.04
	N	**%**	**N**	**%**
Sex				
F	36	1.7	71	1.7
M	2,069	98.3	3,990	98.3
Ore Type				
Hematite only	531	25.2	1,030	25.3
Taconite only	769	36.5	1,554	38.3
Taconite & Hematite	805	38.3	1,477	36.4
Decade of Birth				
1920-1929	1,405	66.7	2,724	67.1
1930-1939	496	23.5	961	23.6
1940-1949	143	6.8	264	6.5
1950-1960	61	2.9	112	2.8

[a]Cases are defined by IHD as an underlying cause of death

The average employment duration of those working in taconite was approximately 12 years (cases: mean=11.9 years, SD=10.0; controls: mean=12.2 years, SD=10.4) (**Table 5**). Of the cases who worked in taconite, the three departments with the greatest number of workers were mining (n=815), shop mobile (n=739), and pelletizing (n=409) (**Table 5**). The departments with the greatest average employment duration among cases were office/control room (mean=7.9 years, SD=8.0), followed by mining (mean=6.8 years, SD=8.1) and shop mobile (mean=6.8, SD=7.5) (**Table 5**). Average cumulative respirable dust exposure was slightly lower among cases (2.55 mg/m^3*years, SD=2.28) than controls (2.60 mg/m^3*years, SD=2.38) (**Table 5**). Additionally, average cumulative respirable silica was the same between cases (0.30 mg/m^3*years, SD=0.29) and controls (0.30 mg/m^3*years, SD=0.29) (**Table 5**). Descriptive characteristics, as well as characteristics of employment and exposure, were similar among IHD underlying/contributing cases and controls (**Supplemental Table 4**).

Table 5. Employment Duration by Industry and Department, and Cumulative Respirable Dust and Respirable Silica Exposures, Respectively, Among Ischemic Heart Disease (IHD) Cases[a] and Controls

	Employment Duration (in years)					
	Cases			**Controls**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
By Industry[b]						
Taconite	1,574	11.9	10.0	3,031	12.2	10.4
Hematite	1,336	5.3	7.0	2,507	4.6	6.1
By Department						
Mining	815	6.8	8.1	1,369	6.5	8.0
Crushing	287	2.0	3.6	513	1.9	3.7
Concentrating	260	3.8	5.4	526	3.6	5.1
Pelletizing	409	2.6	5.1	710	3.7	6.6
Shop mobile	739	6.8	7.5	1,408	7.5	8.4
Shop stationary	333	5.8	7.4	703	6.6	7.9
Office/Control Room	130	7.9	8.0	329	8.0	8.0
Laborer	199	1.6	4.2	388	1.4	3.8
Ore Dressing	88	3.0	5.8	155	3.4	6.1
Unknown[c]	303	6.4	6.5	561	6.6	6.6
	Respirable Exposures (in mg/m^3*years)					
	IHD Cases			**Controls**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Respirable Dust (RD)	1,574	2.55	2.28	3,031	2.60	2.38
Respirable Silica (RS)	1,557	0.30	0.29	2,996	0.30	0.29

[a]Cases are defined by IHD as an underlying cause of death
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive
[c]Unknown includes any individual who did not have a definitive job title or department (excludes laborer department)

Regression Analyses

<u>*Employment Duration*</u>

After accounting for employment duration within each department, taconite workers who worked in mining had a slightly elevated risk of IHD mortality for each year they worked (HR = 1.01; 95% CI = 1.00, 1.02) (**Table 6**). When investigating the association by industry using cumulative years working in taconite (regardless of department) and total years in hematite, no association was found between employment duration in taconite and IHD (HR = 1.00; 95% CI = 0.99, 1.00) (**Table 6**). Cumulative employment duration in production and non-production departments adjusting for employment in unknown departments (including the laborer department) and hematite was also modeled. The results suggested that non-production departments have a slightly decreased risk of death due to IHD for each year worked in the non-production area (HR = 0.99, 95% CI = 0.98, 0.99) (**Table 6**). For each of the continuous models, those who worked in hematite also experienced a slightly elevated risk of IHD mortality for each year of hematite work (**Table 6**). However, no increased risk of IHD was identified for each year of work in a production department (**Table 6**).

Table 6. Risk of Ischemic Heart Disease (IHD) Mortality[a] due to Underlying Cause by Cumulative Employment Duration (in years)

Cumulative Years of Employment	Hazards Ratio	95% CI
By Departments		
Concentrating	1.00	0.97, 1.02
Crushing	1.02	0.98, 1.05
Mining	1.01	1.00, 1.02
Office/Control Room	0.98	0.96, 1.00
Pelletizing	0.98	0.96, 1.00
Shop Mobile	0.99	0.98, 1.00
Shop Station	0.98	0.97, 1.00
Ore Dressing	1.00	0.96, 1.04
Laborer[b]	1.00	0.96, 1.04
Unknown[c]	0.99	0.97, 1.01
Hematite	1.02	1.01, 1.03
By Industry[d]		
Taconite	1.00	0.99, 1.00
Hematite	1.02	1.01, 1.03
By Production Departments		
Production	1.00	1.00, 1.01
Non-Production	0.99	0.98, 1.00
Laborer[b] & Unknown[c]	0.99	0.98, 1.01
Hematite	1.02	1.01, 1.03

[a]Cases are defined by IHD as an underlying cause of death
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive
[c]Unknown includes any individual who did not have a definitive job title or department as well as any workers who were in the laborer department
[d]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive

Utilizing categorical variables, the current study did not identify a pattern of an increase in mortality due to IHD underlying in any of the quartiles of taconite employment as compared to the first quartile (**Table 7**). Additionally, no pattern was found for increased risk of mortality due to IHD as the quartiles of employment duration within production departments increased as compared to the first quartile of employment duration within production departments (**Table 7**). However, there was a decreased risk of death among non-production/unknown workers as compared to the first quartile of employment duration among production workers (IHD underlying: HR = 0.81, 95% CI = 0.67, 0.97) (**Table 7**).

Table 7. Risk of Ischemic Heart Disease (IHD) Mortality[a] by Quartiles of Cumulative Employment Duration (in years)

	Hazards Ratio	95% CI
Quartiles of Cumulative Employment Duration in Taconite[b]		
Taconite Q1 (ref)		
Taconite Q2	0.94	0.79, 1.11
Taconite Q3	1.11	0.94, 1.33
Taconite Q4	0.91	0.77, 1.09
Hematite Only	0.99	0.84, 1.17
Quartiles of Cumulative Employment Duration in Production Departments[c]		
Production Q1 (ref)		
Production Q2	1.16	0.95, 1.43
Production Q3	1.00	0.82, 1.23
Production Q4	1.09	0.88, 1.34
Non-Production	0.81	0.67, 0.97
Hematite Only	0.97	0.81, 1.17

[a]Cases are defined by IHD as an underlying cause of death
[b]Minimum and maximum values for quartiles of cumulative employment duration in taconite (in years) are as follows: Q1=(0.003, 2.491); Q2=(2.500, 9.659); Q3=(9.670, 20.058); Q4=(20.071, 54.031)
[c]Minimum and maximum values for quartiles of cumulative employment duration in production departments (in years) are as follows: Q1= (0.001, 0.975); Q2=(0.977, 3.436); Q3=(3.450, 12.016); Q4=(12.112, 45.240)

For each of the analyses of employment duration, there were very few differences between the estimates and confidence intervals found using IHD underlying versus IHD underlying/contributing (**Supplemental Table 5**). While there were differences in the distribution of quartiles for IHD underlying and IHD underlying/contributing (**Supplemental Table 3**), the estimates and the confidence intervals found for IHD underlying and IHD underlying/contributing in the categorical models (**Table 8** and **Supplemental Table 6**, respectively) followed similar patterns and were not substantively different.

Table 8. Risk of Ischemic Heart Disease (IHD) Mortality[a] by Quartiles of Cumulative Exposure to Respirable Dust and Respirable Silica (in mg/m^3*years)

Quartiles of Cumulative Respirable Dust Exposure[b]	**Hazards Ratio**	95% CI
RD Q1 (ref)		
RD Q2	1.00	0.84, 1.19
RD Q3	1.03	0.86, 1.22
RD Q4	0.99	0.83, 1.19
Hematite Only	1.01	0.86, 1.20
Quartiles of Cumulative Respirable Silica Exposure[c]		
RS Q1 (ref)		
RS Q2	0.96	0.81, 1.14
RS Q3	1.07	0.90, 1.27
RS Q4	1.13	0.94, 1.34
Hematite Only	1.05	0.89, 1.24

[a]Cases are defined by IHD as an underlying cause of death
[b]Minimum and maximum values for quartiles of cumulative respirable dust (in mg/m^3*years) are as follows: Q1=(0.001, 0.622); Q2=(0.623, 1.950); Q3=(1.952, 3.879); Q4=(3.879, 14.228)
[c]Minimum and maximum values for quartiles of cumulative respirable silica (in mg/m^3*years) are as follows: Q1=(0.000, 0.072); Q2=(0.072, 0.233); Q3=(0.233, 0.457); Q4=(0.457, 1.837)

<u>*Respirable Dust*</u>

Cumulative respirable dust exposure (in mg/m^3*years) was not associated with increased risk of death due to IHD among taconite workers (IHD underlying: HR = 0.99;

95% CI = 0.97, 1.02) (**Table 9**). When investigating quartiles of respirable dust exposure, increasing quartiles of exposure, as compared to the first quartile, did not indicate an increased risk of death due to IHD (**Table 8**). Further, the estimates and confidence intervals found for the association between respirable dust and IHD underlying or IHD underlying/contributing did not substantively differ (**Supplemental Table 5 and Supplemental Table 6**).

Table 9. Risk of Ischemic Heart Disease (IHD) Mortality[a] by Cumulative Exposure to Respirable Dust and Respirable Silica

Cumulative Exposure ((mg/m^3)*years)	Hazards Ratio	95% CI
Respirable Dust (RD)	0.99	0.97, 1.02
Respirable Silica	1.02	0.84, 1.24

[a]Cases are defined by IHD as an underlying cause of death

<u>*Respirable Silica*</u>

Increases in cumulative respirable silica exposure (in mg/m^3*years) per year did not suggest increased risk of death due to IHD among taconite workers (HR = 1.02, 95% CI = 0.84, 1.24) (**Table 9**). Risk of death due to IHD appeared to increase with increasing quartiles of silica exposure compared to the first quartile of exposure, but the estimates were included the null value (**Table 8**). The estimates and confidence intervals found for the association between respirable silica and IHD underlying or IHD underlying/contributing were similar and followed similar patterns (**Supplemental Table 5 and Supplemental Table 6**).

Discussion

Although Allen *et al.* found an increased risk of death due to IHD among this taconite mining cohort as compared to the general Minnesota population, the current study did not find evidence of an association between employment duration, cumulative respirable dust exposure, or cumulative respirable silica exposure and IHD mortality (6).

Additionally, based on the current analyses, those who work in non-production departments (i.e., shop mobile, shop stationary, office/control room) appear to have a decreased risk of IHD mortality indicating that exposures in the non-production departments may markedly differ from those in production areas. However, despite these findings, there are risk factors that were not accounted for in this study that could impact IHD mortality in this population. For example, smoking, lipids, hypertension, physical inactivity, and genetics are all risk factors for IHD (23, 46). Using a nested case-control design among a similar population of taconite workers, Allen *et al.* previously suggested that without an adjustment for smoking, associations between exposures including EMPs and respirable silica with health outcomes may be overestimated (5). However, the smoking history of the current study population remain unknown. As a result, given that the smoking history and medical history of the current population is unknown, it is unclear whether the estimates may be differentially or non-differentially affected and it is additionally unclear in which direction the estimate may be driven if smoking and/or medical history was accounted for.

Population-based studies generally utilize measures of particulate matter rather than respirable dust. However, particulate matter and respirable dust share similarities in size and within taconite mining, the two exposures have demonstrated a strong correlation (25). Previous population-based studies have suggested a relationship between particulate matter and cardiovascular outcomes including IHD (**Supplemental Table 7**) (14, 15, 20). However, similar to the many of the findings in the current study, some studies do not suggest an association (54-56). In recent studies by Rodins *et al.*, Ljungman *et al.*, and Thurston *et al.*, no associations were found between particulate matter and ischemic heart disease (54-56).

Rodins *et al.* conducted a prospective population-based study in Germany among 4,105 participants between 45 and 76 years of age at baseline to investigate the association between long-term exposure to particulate matter, including $PM_{2.5}$, and risk of the first occurrence of stroke, coronary heart disease (i.e., IHD), and total cardiovascular events (i.e., stroke and IHD) among study participants followed from 2000 to 2014 using Cox proportional hazards regression (55). Baseline data was collected between 2000 and

2003 and follow up measures were collected at two time points in 2006 to 2008 as well as 2011 to 2015. Residential addresses were used to assign each participant an average concentration of $PM_{2.5}$ at baseline (2001-2003) and follow-up (2006-2008). The maximum average $PM_{2.5}$ exposure at baseline was 22.10 μg/m^3. After controlling for covariates including age, sex, education, employment status, marital status, neighborhood socio-economic status, body mass index, smoking, alcohol consumption, physical activity, nutritional pattern, and nighttime traffic noise exposure, the authors identified an increased risk of stroke per IQR increase of $PM_{2.5}$ (HR=1.39; 95%CI=1.03, 1.84). However, they did not identify an association between IHD and $PM_{2.5}$ (HR=0.89; 95%CI=0.75, 1.05).

Findings were similar in a study by Ljungman *et al.* among 114,758 participants who were between 9 and 92 years old at baseline in a multi-cohort study of Swedish residents between 1990 and 2011 (54). The authors investigated the association between air pollutants, including ambient $PM_{2.5}$, with hospitalization or mortality due to stroke and IHD. Ljungman *et al.* evaluated the association between ambient $PM_{2.5}$ and IHD for three different exposure periods: exposure the same year of the event, 1 to 5 years preceding the event, and 6 to 10 years preceding the event. While the authors identified positive associations between ambient $PM_{2.5}$ for the same year of the event as well as 1 to 5 years preceding the event the confidence interval included the null value for both estimates, and no association was identified between ambient $PM_{2.5}$ and IHD hospitalization or mortality for 6 to 10 years preceding the IHD event.

Additionally, Thurston *et al.* investigated the association between air pollutants and IHD mortality between 1982 and 2004 among 445,860 adults who were at least 30 years of age at baseline across 100 U.S. metropolitan areas (56). $PM_{2.5}$ data were collected for 2000 to 2005 based on the metropolitan statistical area of each participant and were used to estimate average exposure for individuals from 1982 to 2004. Using the fully adjusted model with random effects, the authors determined that for every quartile increase (i.e., 3.145 μg/m^3) in $PM_{2.5}$, the rate of death due to IHD increased by 3%, but the estimate included the null (HR=1.03; 95%CI=1.00, 1.06). Using source apportionment analysis to determine the constituents present in $PM_{2.5}$, the authors determined that the association was driven by constituents including arsenic (HR=1.04; 95%CI=1.02, 1.06), lead (HR=1.03; 95%CI=1.01, 1.04), and selenium (HR=1.03; 95%CI=1.01, 1.06), as well as by coal combustion (HR=1.03; 95%CI=1.01, 1.05).

Although the findings of Rodins *et al.*, Ljungman *et al.*, and Thurston *et al.* align with the findings of the current study, the exposures experienced in each of these previous studies do not reflect the exposures experienced in taconite mining in magnitude nor in composition (57, 58). While Rodins *et al.* determined an association between increases in particulate matter and stroke, strokes affect small vessels whereas IHD is a disease of the large vessels. As a result, Rodins *et al.* findings may reflect the differing pathological effects $PM_{2.5}$ has on small vessels (i.e., stroke) as compared to large vessels (i.e., IHD). Additionally, for Rodins *et al.* and Thurston *et al.*, the authors did not use cumulative exposure, but rather an average concentration of $PM_{2.5}$ to determine risk. As a result, individuals who may have experienced greater exposures over time were not appropriately accounted for, nor were the effects of potential acute exposures able to be captured. Rodins *et al.* and Thurston *et al.* also used exposure measurements taken at the area level near participants' residential address which may not accurately reflect participants' real experiences if they had exposures outside of the area in which they lived. Unlike the Ljungman *et al.* study, the current study does not explore the effect of recent windows of exposure (e.g., same year of the event or 1 to 5 years preceding the event). For the current study, the last exposures were recorded on December 31, 1982 and any subsequent exposures experienced by the workers until their vital status date or the end of follow up in 2010 were not recorded. However, recent windows of exposure may be more appropriate for exploring impacts of $PM_{2.5}$ on hospitalization and/or IHD incidence, whereas longer term, cumulative exposures may be more appropriate for understanding the impact on mortality since mortality may arise due to a culmination of air pollution effects, age, disease severity and comorbidities (54).

Occupational studies have also been conducted to investigate the effects of particulate matter on cardiovascular outcomes (**Supplemental Table 7**) (16, 59). Costello *et al.* investigated the effect of particles (i.e., $PM_{3.5}$) generated from the aerosols of three classes of metalworking fluid (i.e., straight, soluble, and synthetic classes) on IHD mortality among an occupational cohort of metalworkers (59). Unlike soluble and synthetic metalworking fluid, straight metalworking fluid contains polycyclic aromatic hydrocarbons (PAHs), which are associated with adverse cardiovascular outcomes (59). The authors reported an increase in IHD mortality related to cumulative exposure to straight metalworking fluid $PM_{3.5}$ from 1941 to 1994 (highest exposure quantile (>2.77 mg/m^3) HR=1.53; 95%CI=1.15, 2.05) as well as from 1971 to 1994 (highest exposure quantile (>3.40 mg/m^3) HR=1.64; 95%CI=1.12, 2.41) using employed person-time. No associations were found between straight metalworking fluid $PM_{3.5}$ and IHD mortality from 1941 to 1970. Costello *et al.* attributed the association between cumulative exposure of straight metalworking fluid $PM_{3.5}$ and IHD mortality to the presence of PAHs, which is not present in soluble or synthetic metalworking fluid $PM_{3.5}$. However, no trend was found between increased exposure to straight metalworking $PM_{3.5}$ and increased IHD mortality. Further, the composition of particulate matter in metalworking differs from the composition of particulate matter and respirable dust within the taconite industry (57, 58). As a result, the findings of Costello *et al.* may not be comparable to those found among taconite workers.

Neophytou *et al.* investigated the risk of a first IHD event (i.e., first occurrence of IHD whether death or incidence) due to $PM_{2.5}$ exposure among aluminum fabricators and smelters (60). Using a traditional Cox model, the authors found that smelting and fabricating experienced similar risk of IHD, despite the higher exposure among smelters (fabricators: HR= 1.24; 95%CI= 0.92, 1.68; smelters: (approximated from Figure 2) HR=1.60; 95%CI=1.1, 2.5) (60). To determine whether the presence of time-varying confounding was the cause of the null association among smelters, the authors utilized marginal structural models (MSMs) to account for changes in health status that affected subsequent exposure and, as a result, incident IHD. The authors found that when utilizing MSMs, the risk of incident IHD increased among smelters (HR=1.98; 95%CI= 1.18, 3.32), indicating the presence of the healthy worker survivor effect (HWSE). However, utilizing MSMs resulted in a similar estimate for fabricators (HR= 1.34; 95%CI=0.98, 1.83). Similarly, in the present study, it is possible that the HWSE has attenuated the association between respirable dust and IHD. However, the present study lacks information on health status, which prevents conducting an analysis (e.g., using MSMs) that may account for time-varying confounding. Additionally, the current study focuses on mortality, but given that Neophytou *et al.* combined both incident cases and cases of mortality due to IHD, the estimates presented in the Neophytou *et al.* paper may be greater than what would be expected from a study of mortality alone.

In addition to the effects of respirable dust on IHD mortality among taconite workers in Minnesota, the current study also explored the effect of respirable silica on IHD mortality. In an animal study, silica exposure elicited pulmonary inflammation and damage that increased over time along with the development of fibrosis even after silica exposure had ceased (61). Another animal study also found an increase in inflammatory markers (e.g., C-reactive protein, interleukin-6) after intratracheal installation of ultrafine silica nanoparticles in rats and determined that plasma levels of D-dimer and endothelin-1 (ET-1), which are related to cardiovascular effects including myocardial infarction and atherosclerosis, were increased even after exposure to low concentrations of silica particles (62). However, epidemiologic studies investigating the effects of silica components in respirable dust have found varying results.

Lai *et al.* investigated the association between cumulative respirable silica and a variety of mortality outcomes, including IHD, among an occupational cohort of Chinese iron miners (63). The authors collected retrospective on a total of 7,665 workers who were followed from 1960 until 2012. Respirable dust concentrations in the mine were collected monthly by the Chinese government. The authors used data collected from a field study that determined the percentage of silica present in the respirable dust to estimate historical silica exposures and then used a JEM to estimate silica concentrations for each worker over time and calculate each worker's cumulative exposure to respirable silica. The authors also collected data on smoking. Using Cox proportional hazard models and adjusting for gender, year at hire, age at hire, and smoking, the study found a positive association with IHD mortality and an increase of 1 mg/m^3*year increase in cumulative respirable silica, however, the 95% confidence interval included the null value (HR=1.134; 95%CI=0.990, 1.298). Associations were also explored for quartiles of silica exposure (i.e., unexposed, low (0.4935 mg/m^3*y or below), medium (0.4935 to 0.8423 mg/m^3*y), high (0.8423 mg/m^3*y or above)) in comparison to those who were unexposed. The authors did not find a precise association for the lowest quartile of cumulative silica exposure (HR=1.190; 95%CI=0.738, 1.918). However, there was an increased risk of IHD mortality found among workers within the medium (HR=1.538;95%CI=1.063, 2.226) and high quartiles (HR=1.781; 95%CI=1.281, 2.476) of silica exposure and the trend between low, medium, and high quartiles of exposure was significant ($p<0.001$). While the authors identified an association in the medium and high quartiles of respirable silica exposure, the cumulative exposures experienced by Chinese iron miners differed from those experienced by Minnesota taconite miners. Although the range of exposures within the Chinese miners is like the range within Minnesota taconite miners, a larger proportion of Chinese miners experienced higher exposures to respirable silica than found among Minnesota taconite miners. As a result, it is not unusual that even within the highest quartile of the current study among Minnesota taconite miners, no association was found, but within the medium and high exposure groups of the Lai et al (2018) study, associations between cumulative respirable silica and IHD were identified. Additionally, for the current study, no adjustments for smoking were made, but if the adjustment had been made, the estimates would likely be further attenuated.

In a study conducted by Wang *et al.* among metal mines and pottery factories in China, the association between cumulative respirable silica exposure and cigarette smoking with mortality was explored among 44,708 workers (64). Using data collected on employees' work histories from 1950 through 2003 and historical and current silica concentrations a job exposure matrix was developed to determine each individual's cumulative respirable silica dust exposure ($mg/m^3*years$). Smoking histories were collected in 1986, 1995, and 2004 or from colleagues or next of kin to determine smoking status (ever/never). Mortality was based on ICD-10 codes. Hazard ratios and 95%CIs were calculated using Cox proportional hazards models between cumulative silica exposure and selected causes of death after adjusting for sex, year of hire, age at hire, type of facility, and smoking history. Cumulative respirable silica exposure was divided into tertiles (low, medium, and high). Compared to those who were never exposed to silica dust, there was not an increased risk of ischemic heart disease among those who had been exposed to low (0 to 1.056 mg/m^3*years; HR=1.20; 95%CI=0.94, 1.55), medium (1.057 to 3.925 mg/m^3*years; HR=1.21; 95%CI=0.95, 1.54) or high (>3.925 mg/m^3*years; HR=0.77; 95%CI=0.58, 1.01) levels of silica dust, respectively, after controlling for sex, year at hire, age at hire, type of facility, and smoking intensity. Wang *et al.* also investigated a non-linear relationship between cumulative respirable silica exposure and cardiovascular disease mortality using a spline model and found that risk of cardiovascular disease mortality increased with increasing silica exposure. However, the relationship between cumulative silica exposure and ischemic heart disease was not reported. Further, while an increased risk was found between cumulative respirable silica dust exposure with cardiovascular disease mortality, the association was largely driven by the association between silica dust and pulmonary heart disease mortality, not ischemic heart disease mortality. Additive interaction between silica exposure and smoking with mortality due to ischemic heart disease was not identified (relative excess risk due to interaction=-0.17; 95%CI=-0.95, 0.81).

Liu *et al.* conducted a meta-analysis of occupational studies to assess the association between respirable silica and heart disease, including IHD. The authors identified 14 studies investigating the association between respirable silica and IHD between January 1995 and June 2019 and found a modest association, however, this association included the null (meta-RR=1.07; 95%CI=1.00, 1.16). As in the current study, the association found was slightly increased. Thurston *et al.* also explored the association between components of $PM_{2.5}$, including silica, and IHD mortality, but did not find an association between interquartile increases of silica (IQR=42.9) and IHD mortality (HR=0.99; 95%CI=0.97, 1.02).

Although the current study did not identify an association between respirable dust or silica with IHD, there were limitations. While exposure estimates for respirable dust and respirable silica were reconstructed using available historical data and personal sampling data, exposure data was not collected for all SEGs and gaps in historical exposure data existed (3, 58). Additionally, to reconstruct historical data, a regression model and imputation were used and a linear trend in historical exposure was assumed (58). Given the incomplete exposure data and the assumption of a historical linear trend, it is possible that exposures were misclassified.

It is also possible that misclassification of job titles may have also occurred. Although work history records were standardized to the extent possible, job titles within the employment record were often incomplete or difficult to interpret. As a result, it is possible that job titles were assigned to the incorrect SEG, and therefore the incorrect department resulting in employment duration and exposure misclassification. However, this misclassification was likely non-differential (i.e., it was unrelated to being a case or control).

Despite the limitations of the exposure data in the current study, employment duration data are less likely to be biased and may serve as a proxy for exposures that are present within taconite mining, including exposures related to respirable dust and respirable silica. However, results between employment duration and IHD mortality were similar to those using exposure data in the current study, i.e., there was little evidence of an association between employment duration and IHD mortality.

Studies have demonstrated that IHD mortality increases with high temperatures as well as with low temperatures (65). However, the current study does not consider effects of temperature (heat or cold) or noise despite both potentially playing a role in mortality due to IHD. Additionally, Davies *et al.* also identified occupational noise as a potential risk factor for IHD mortality and the current study does not adjust or consider the role of occupational noise in relation to IHD mortality (66).

Additionally, smoking was not adjusted for in the analyses. Based on a previous study among a similar population of taconite workers, Allen *et al.* determined that smoking status differed based on exposure status and it is likely that in the current study that may be the case as well. Specifically, more exposed workers may be more likely to smoke than those who experienced less exposure and given the time period, smoking was also more prevalent. Further, smoking is also associated with the outcome (i.e., IHD mortality). Although it is possible that this would bias the results toward the null if unmeasured confounding due to smoking was present, given that smoking history was not collected for all participants in the current study, the direction of bias remains unknown.

One potential reason the current study did not identify an association between respirable dust or respirable silica with IHD mortality may be due to the healthy hire effect. That is, individuals who were placed in jobs that were more highly exposed were healthier than those who were placed in lower exposure jobs; therefore, there may not be an association among highly exposed individuals since they were already at lower risk for IHD mortality. Despite lack of information on lifestyle, there was information on department, and no significant differences were observed by department indicating that it is possible that the healthy hire effect did not impact the results of this study.

The current study also had a number of strengths. This is the first study to investigate the relationship between respirable dust and respirable silica with IHD mortality within this taconite cohort. Despite evidence that exists linking fine particulate matter to increased cardiovascular disease morbidity and mortality in population-based studies, few studies have investigated the extent to which fine particulate matter or respirable dust, which are closely correlated within the current study population, contribute to cardiovascular outcomes within occupational cohorts (15, 16, 25, 51). However, population-based studies are often limited to the use of ambient measures of $PM_{2.5}$ that are generally limited to large areas such as census tracts or county-level measures within which there can be high variation in exposure. Additionally, population-based studies are generally cross-sectional whereas the current study utilizes a large cohort with exposure metric estimates that have been modeled over time and are informed by both personal and historical samples. As a result, unlike population-based studies that focus on short periods of exposure, the current study provides an opportunity to determine the potential effects of cumulative exposure to respirable dust over an individual's entire work history.

When underlying causes of death are due to chronic diseases that may have co-occurring comorbidities, utilizing the contributing cause of death may provide additional insight into the effect of working in taconite on IHD mortality (33). Although misclassification of the underlying cause of death is possible when chronic diseases such as COPD and IHD are comorbidities, given the similarity of results between IHD underlying and IHD underlying/contributing, there is little evidence of misclassification of IHD within the current cohort between the use of underlying or contributing causes of death.

Further, the study sample was large and as a result the estimates were generally precise when estimating the effects of exposures associated with IHD mortality. Lastly, despite the difficulties with work history abstractions and job titles, relying on work histories to define worker's exposure eliminates the potential for recall bias if instead workers or their families had been questioned about their roles in taconite mining.

Conclusion

The current study did not identify associations between IHD mortality and employment duration or exposures within taconite mining. Although miners experience unique exposures that often occur at higher levels than the general population, the results of this study suggest that occupational factors are unlikely to lead to increased IHD mortality.

Chapter 4: Chronic Obstructive Pulmonary Disease Mortality among Minnesota Taconite Mining Industry Workers

Introduction

Chronic obstructive pulmonary disease (COPD) is classified as a group of diseases including emphysema and chronic bronchitis that cause airflow obstruction (22, 46, 67). Although smoking is a primary risk factor for COPD development and progression, other risk factors include environmental and occupational air pollutants as well as genetic factors, age, and prior respiratory infections (22, 46, 67). Moreover, COPD often occurs concurrently with ischemic heart disease (IHD), and individuals with COPD and comorbid IHD experience greater adverse health effects (e.g., breathlessness, lowered exercise capacity, and poorer health status) than those with COPD alone (22, 68, 69).

In Minnesota, iron ore mining has been an integral part of the state's economy since the early 20th century (49). Following the depletion of high-grade hematite iron ore, the mining of taconite, a lower grade iron ore which requires processing for use in steel production, became the predominant iron ore source for North America in the latter half of the 20th century (2). Taconite mining involves blasting rock from open pits and then crushing and processing the rock in order to extract iron ore (2, 3). Since taconite mining and processing can result in several potentially harmful exposures, including elongate mineral particles (EMPs), respirable silica, and respirable dust, concerns about health effects of occupational exposures have led to studies of taconite miners (2, 4-10). Although a previous mortality study among this population did not demonstrate increased mortality due to COPD using standardized mortality ratios (SMRs) (SMR=0.98; 95%CI=0.88, 1.09), a more recent study among iron foundry workers identified an association between COPD morbidity and respirable dust and respirable silica standardized incidence ratios (SIRs) (6). Additional occupational studies among varying industries have found associations between respirable dust (aerodynamic diameter ≤4μm) and respirable silica with COPD and IHD outcomes (14, 15, 20, 50, 51). Further, exposure to amphibole and non-amphibole elongate mineral particles (EMPs) has also been identified among the current cohort of taconite miners and may be included as a component of respirable dust (11, 27).

Environmental factors such as $PM_{2.5}$ have also been associated with COPD and have been shown to initiate systemic inflammation and oxidative stress in murine models. In population-based epidemiologic studies, $PM_{2.5}$ has been found to alter pulmonary vasculature leading to the development of COPD (18-20). Although $PM_{2.5}$ and respirable dust are different sized particles, previous work conducted by Huynh *et al.* within taconite mining found that $PM_{2.5}$ and respirable dust exposures within the mines were highly correlated (25).

To determine whether working in taconite affects COPD mortality, the current study investigated the effects of employment duration, respirable silica, and respirable dust exposure on mortality related to COPD. In addition to the primary objective, an exploration of potential misclassification of COPD as an underlying cause of death was also undertaken since reliance on solely the underlying cause of death may lead to misclassification when co-morbidities such as IHD are present (33). Because of this concern, a secondary objective was to evaluate the potential misclassification of COPD as an underlying cause of death by identifying contributing causes of COPD mortality where IHD was classified as the underlying cause of death.

Methods

Study Design & Population

We conducted a nested case-control study within a cohort of iron mining workers. In 1983, employee records for 68,737 workers were collected from seven existing taconite mines as part of the Mineral Resources Health Assessment Program (MRHAP), a collaboration between the Iron Range Resources and Rehabilitation Board and the University of Minnesota's School of Public Health, to investigate the health effects taconite workers may experience due to occupational exposures. In 2008, the health assessment of these taconite workers was updated as part of the University of Minnesota's Taconite Workers Health Study (TWHS). As part of this update, the vital status of each of the workers was obtained through 2010 by utilizing data from the National Death Index, Social Security Administration, Minnesota Department of Health and state death certificates for individuals who expired outside of Minnesota. International Classification of Disease (ICD) codes that were in effect at the time of death were used.

While the exposures of interest for this study are from taconite mining and processing, this cohort included both hematite and taconite workers. To focus on taconite mining, which began in the 1950s, workers who were born in 1920 or later were included in the current study (N=46,170). Additional exclusions included cohort members whose employment record was limited to an application (N=477), for whom vital status could not be ascertained (N=679), and were likely not employed (e.g., those younger than 14 at the time of employment) (N=539). Further, individuals who died prior to 1960 were also excluded (n=232) since mortality data was not as comprehensive prior to that year. To ensure the current study focused on workers with more stable employment in the industry (i.e., not summer workers or temporary workers), workers who worked less than 1 year were also excluded (n=13,176). In total, cases and controls were selected from 31,067 workers included in the current cohort.

Selection of Cases & Controls

The primary objective was to determine the association between several work characteristics among taconite miners (i.e., employment duration, respirable silica, and respirable dust exposure) and COPD mortality. Given that reliance on the underlying cause of death alone may lead to misclassification when co-morbidities such as IHD are present, a secondary objective was to determine the potential misclassification of COPD as an underlying cause of death by including contributing causes of COPD mortality where IHD was classified as the underlying cause of death (26). As a result, cases were defined in two ways based on how COPD was listed on the death certificate: 1) COPD underlying and 2) COPD underlying/contributing. COPD underlying cases included cases identified as COPD from the underlying cause of death listed on the death certificate. COPD underlying/contributing cases included *all* COPD underlying cases *in addition to* COPD cases identified as contributing causes on the death certificate with IHD as an underlying cause on the death certificate.

As noted above, cases included all decedents with COPD as the underlying cause of death (COPD underlying: N=363) based on NIOSH-119 designations (**Supplemental Table 1**) (41). A secondary set of COPD cases was identified where IHD was the underlying cause of death and COPD was a contributing cause of death to explore the potential for misclassification of COPD (COPD contributing: N=136; COPD underlying/contributing: N=499).

For each case, two controls were randomly selected using an incidence density sampling scheme. The controls were selected from risk sets of all cohort members alive at the year of death of the case and matched on birth year (+/- 2 years) and sex.

Work History Abstractions

Work history abstractions for each case and control were completed to gather information for each workers' employment history. These records included information on workers' specific job titles, their start and end dates for each position they held, and the mining company (i.e., mine) for which they worked. Each workers' job title was standardized and then grouped into previously established similar exposure groups (SEGs) (3, 5, 9, 12). If job and department information was not available, the job title was assigned to an "unknown" SEG.

The SEGs were then grouped into specific departments. Additionally, for work histories that did not have job titles, department information was used to map workers to the appropriate department. Hwang *et al.* and Shao *et al.* created job exposure matrices based on 8 departments including: mining, crushing, concentrating, pelletizing, shop mobile, shop station, office/control room, and janitor (3, 12). However, for the current study, janitors had the smallest department in the current study compared to other groups and were assigned to shop(mobile). The current study also included 3 additional departments: ore dressing, laborer, and unknown. Ore dressing is a department that was not used in previous studies, but encompassed work done in both crushing and concentrating. The laborer category included job titles that indicated the worker was in an “assigned labor” position, for example, but did not have a specific department identified in the employment records. The unknown category encompassed job titles that could not be mapped to an SEG and for which the department could not be identified, or the worker only had employment information related to the mine, but no information on the work conducted by the worker (i.e., no job title information was available).

Finally, while most workers worked in taconite, some workers included in the study worked in both hematite and taconite, and some worked in only hematite. Since exposures experienced in hematite were different than those experienced in taconite, a final department, hematite was created to separate hematite work history from taconite work history. If a workers’ start date for a particular job title began prior to the start of taconite for that specific mine or if their job title indicated that they worked in hematite (e.g., a job title of “underground”), they were assigned to a hematite department.

Exclusions to cases and controls were made if there was no evidence that an individual worked in hematite or taconite mining. After these exclusions, if cases or controls no longer had at least one match, these workers were also dropped from the study. This led to 349 cases and 669 controls for the analysis of COPD as an underlying cause of death (i.e., COPD underlying), with only one control per case for 29 cases and two controls per case for the remaining 320 cases. For the secondary analysis that included contributing causes of COPD (i.e., COPD underlying/contributing), after these exclusions, there were 483 cases and 929 controls remaining, with only one control per case for 37 cases and two controls per case for the remaining 446 cases.

Employment Duration

To calculate employment duration, the start and end dates for each position held by each worker for each job were used. For a particular job title, if no start or end date was recorded, that particular job was dropped from the analyses. Similarly, if the start and end date were the same for a particular job title, these jobs were also dropped from the analyses. After these exclusions, all workers had a known start date for the first position that they held within the mine. For unknown start dates with an end date, the day after the previous job's end date was imputed as the start date. For known start dates with unknown end dates, the day before a subsequent job's start date was imputed as the end date. For known start dates with unknown end dates that served as the last position held for a worker, the end date was imputed in two ways. For controls with an unknown end date, the vital status date of the case was imputed as the end date. Otherwise, December 31, 1982 was imputed as the end date since employment information was not captured from 1983 onward.

For each worker, cumulative employment duration was calculated by adding the total time (in years) each worker spent within a specific department (i.e., mining, crushing, concentrating, ore dressing, pelletizing, shop mobile, shop stationary, laborer, office/control room, and unknown). Cumulative employment duration was also calculated for those working in hematite. Additionally, a production variable which was the cumulative employment duration (in years) for those working in mining, crushing, concentrating, ore dressing, and pelletizing was also created along with a non-production variable which was the cumulative employment duration (in years) of those working in non-production areas (i.e., shop mobile, shop stationary, office/control room).

Respirable Dust and Respirable Silica Exposure

The mineralogical composition of the rock differs by the location of the mines in the Mesabi Iron Range with mines in the eastern zone having a different geology than those in the western zone, as a result, the exposures experienced due to processing these rocks may differ (3, 11, 52, 53). To characterize respirable dust and silica exposures within the mines, Hwang *et al.* collected personal air samples from active mines in the Mesabi Iron Range including one mine in the eastern zone and five mines in the western zone between 2010 and 2011 (3, 11, 52). Hwang *et al.* selected workers within each SEG at each mine to collect samples using personal air sampling pumps (3). Hwang *et al.* further classified each SEG into a department except for janitors whose exposure profile differed from other departments (3).

Mine specific exposures collected by Hwang *et al.* were used by Shao *et al.*, in addition to historical personal and area samples, to reconstruct respirable dust and silica exposures from 1955 to 2010 (12). The reconstructed respirable dust and silica exposures calculated by Shao *et al.* were then placed into a job exposure matrix by year (1955 to 2010), mine, and department (12).

To estimate the respirable dust and silica exposure experienced by each worker within each department, the information collected from employment duration was combined with the reconstructed exposure data from Shao *et al.* (12). Cumulative respirable dust and silica exposure were estimated by multiplying respirable dust and silica for each year, mine, and department by the respective employment duration identified for each worker by year, mine, and department. The summation of these products was used to determine cumulative exposure for each worker in (mg/m^3)*years for respirable dust and respirable silica, respectively.

To calculate exposures for the “unknown” department, respective mine average estimates for all 8 departments by year were used. For those assigned to the “ore dressing” department, exposures were calculated based on the average exposures within the crushing and concentrating departments combined. Exposures for the laborer category were based on the average of all non-office departments (i.e., mining, crushing, ore dressing, concentrating, pelletizing, shops(stationary), and shops(mobile)). Since the exposure profile of janitors differed from that of other departments, Shao *et al.* grouped them into their own department (12). However, in the current study, janitors were assigned shop(mobile) exposure. In conclusion the following departments were utilized for respirable dust and silica exposure: mining, crushing, concentrating, ore dressing, pelletizing, shop mobile, shop stationary, office/control room, laborer, and unknown.

Further, in some cases, exposure data for a particular mine was not available if the mine was a taconite mine prior to 1955. In these cases, the all mine averages by department from 1955 were used to estimate exposures prior to 1955.

Descriptive Characteristics

Population Characteristics

For 1) the COPD underlying cause of death analysis (COPD underlying) and 2) the COPD underlying or contributing cause of death (COPD underlying/contributing) analysis, characteristics of cases and controls were described by average year of birth, sex (male, female), and the ore type in which each worker worked (hematite only, taconite only, taconite & hematite). Characteristics were also described for each case and control by decade of birth.

Employment Duration

For COPD underlying and COPD underlying/contributing analyses, employment duration was described by the average number of cumulative years employed in any taconite or hematite industry as well as the average number of cumulative years employed in any department. Employment duration was also presented as the average number of cumulative years employed in production and non-production departments (**Supplemental Table 8**).

Quartiles of total employment duration in taconite and quartiles of total employment duration in production departments were also created based on the distribution of the cases for COPD underlying and COPD underlying/contributing, respectively (**Supplemental Table 9**).

<u>Respirable Dust and Respirable Silica Exposures</u>

Cumulative respirable dust and respirable silica exposures were determined for cases and controls by the combined exposures to these dusts for each SEG worked (in mg/m^3*years). Separate quartiles for cumulative respirable dust and respirable silica exposure were created based on the distribution of the exposure for cases for both COPD underlying and COPD underlying/contributing, respectively (**Supplemental Table 9**).

Regression Analyses

Conditional logistic regression was used to estimate the hazard rations (HR) and 95% confidence intervals to characterize the association between employment duration, respirable dust, and respirable silica exposure with COPD mortality. Since controls were obtained using incidence density sampling, risk sets were created, and as a result, the estimates from the models of this case control study can be interpreted as hazard ratios.

Models were estimated separately for associations between employment duration, as well as for associations between cumulative exposure for respirable dust and respirable silica with 1) COPD underlying and 2) for COPD underlying/contributing.

Controls were selected based on birth year (+/- 2 years) and sex, limiting the possibility of residual confounding given the close caliper matching for birth year, age, and sex. The independent variables of employment duration and cumulative exposure for respirable dust and respirable silica were included in each model as continuous variables and categorical variables to describe taconite workers' employment duration and cumulative exposure experience.

For employment duration (in years), risk estimates were initially adjusted for number of years spent within each department, including hematite. A separate model was created by utilizing a continuous variable for any employment in taconite (in years) as well as employment in hematite (in years). Lastly, a model accounting for employment duration within production and non-production departments, as well as unknown departments (which included the laborer department) and hematite was created.

Employment duration was also described and modeled categorically using two models. By using categorical designations of a continuous variable, the effect of potential outliers on the model are reduced and it can assist in determining trends with increasing exposures. One model categorized employment duration into five categories including four categories representing quartiles of cumulative employment duration in taconite and the last category representing employment within hematite only. The second model categorized employment duration into six categories including four categories representing quartiles for production, as well as a category for non-production only (which included unknowns), and hematite only.

Associations between cumulative respirable dust (mg/m^3*years) and respirable silica (mg/m^3*years) with COPD mortality were first accounted for by utilizing a continuous variable for overall cumulative exposure (where hematite exposure was represented as no exposure, i.e., 0 mg/m^3*years) for each exposure, respectively.

Unlike continuous exposure variables, categorical classifications of exposure do not ascribe a particular exposure-response curve to the data. Further, categorization of exposure may provide insight into potential levels of exposure at which there are no observed adverse effects and assist in understanding whether there is an increasing effect with increases in exposure levels or a trend within each category of exposure. Specifically, categorical classifications may also help determine if there is a level at which no adverse effect occurs. As a result, associations between cumulative respirable dust (mg/m^3*years) and respirable silica (mg/m^3*years) exposures were also described and modeled categorically. The categorical model categorized exposure into five categories including four categories representing quartiles of cumulative respirable dust and cumulative respirable silica, respectively, and the last category represented those who were employed within hematite only (i.e., they had zero respirable dust or respirable silica exposure due to work within the taconite industry).

Results

Characteristics of Cases and Controls

For COPD underlying, most of the total cases and controls were male (cases: n=334, 95.7%; controls: n=642, 96.0%) (**Table 10**). The distribution of employment across hematite and taconite was similar among cases and controls (**Table 10**). The average birth year for cases and controls was 1927 (**Table 10**).

Table 10. Characteristics of Chronic Obstructive Pulmonary Disease (COPD) Cases[a] and Controls

	Cases		Controls	
	Mean	**SD**	**Mean**	**SD**
Birthyear	1927	6.2	1927	6.1
	N	**%**	**N**	**%**
Sex				
F	15	4.3	27	4.0
M	334	95.7	642	96.0
Ore Type				
Hematite only	86	24.6	173	25.9
Taconite only	130	37.4	235	35.1
Taconite & Hematite	133	38.1	261	39.0
Decade of Birth				
1920-1929	243	69.6	464	69.4
1930-1939	87	24.9	171	25.6
1940-1949	16	4.6	28	4.2
1950-1960	3	0.9	6	0.9

[a]Cases are defined by COPD as an underlying cause of death

The average employment duration of those working in taconite was approximately 12 years (cases: mean=11.5 years, SD=10.3; controls: mean=12.0 years, SD=10.7) (**Table 11**). Of the cases who worked in taconite, the two departments with the greatest number of workers were mining (n=115) and shop mobile (n=97) (**Table 11**). The departments with the greatest average employment duration among cases occurred among those with unknown departmental work histories (mean=9.0 years; SD=7.9), followed by shop mobile (mean=7.6 years, SD=8.8) and mining (mean=7.1 years, SD=8.8) (**Table 11**).

Average cumulative respirable dust exposure was slightly lower among cases (2.3 mg/m^3*years, SD=2.3) than controls (2.5 mg/m^3*years, SD=2.5) (**Table 11**). Average cumulative respirable silica was also similar between cases (0.3 mg/m^3*years, SD=0.3) and controls (0.3 mg/m^3*years, SD=0.3) (**Table 11**).

Table 11. Employment Duration by Industry and Department, and Cumulative Respirable Dust and Respirable Silica Exposures, Respectively, Among Chronic Obstructive Pulmonary Disease (COPD) Cases[a] and Controls

	Employment Duration (in years)					
	Cases			Controls		
	N	Mean	SD	N	Mean	SD
By Industry[b]						
Taconite	263	11.5	10.3	496	12.0	10.7
Hematite	219	5.6	8.1	434	4.4	6.1
By Department						
Mining	115	7.1	8.8	213	6.4	8.2
Crushing	39	1.8	3.6	76	1.6	3.3
Concentrating	40	2.9	4.5	76	2.9	5.5
Pelletizing	59	3.0	6.1	100	3.4	6.6
Shop mobile	97	7.6	8.8	231	8.9	8.9
Shop stationary	54	4.4	5.6	97	6.7	8.6
Office/Control Room	35	6.9	8.7	50	9.9	10.3
Laborer	44	2.1	6.1	44	1.7	4.4
Ore Dressing	4	0.4	0.5	17	3.5	8.2
Unknown	59	9.0	7.9	83	6.7	6.5
	Respirable Exposures (in mg/m^3*years)					
	COPD Cases			**Controls**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Respirable Dust	263	2.3	2.3	496	2.5	2.5
Respirable Silica	263	0.3	0.3	496	0.3	0.3

[a]Cases are defined by COPD as an underlying cause of death
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive

Descriptive characteristics, as well as characteristics of employment and exposure, were similar among COPD underlying/contributing cases and controls except for the departments with the greatest average employment duration (**Supplemental Table 10**). Among COPD underlying/contributing cases, departments with the greatest average employment duration among cases occurred among those who worked in the office/control room (mean=8.1 years; SD=9.1), followed by those who had unknown departmental work histories (mean=7.3 years; SD=7.0) and those who worked in the shop mobile department (mean=6.9 years, SD=7.7).

Regression Analyses

Employment Duration

After accounting for employment duration within each department, taconite workers who worked in the mining department had a slightly elevated risk of COPD mortality for each year they worked although the result included the null value (i.e., 1.00) (HR = 1.01; 95% CI = 0.98, 1.03) (**Table 12**). When investigating the cumulative years working in taconite (regardless of department) and total years in hematite, no association was found between employment duration in taconite and COPD (HR = 0.99; 95% CI = 0.98, 1.01) (**Table 12**). However, cumulative years working in hematite was elevated, but included the null value (HR=1.03; 95%CI=1.00, 1.05). Cumulative employment duration in production and non-production departments adjusting for employment in unknown departments (including the laborer department) and hematite was also modeled. The results suggested that there was no significantly increased risk of COPD among production or non-production departments, nor those who worked in hematite. There was a 4% increased risk of death due to COPD for each year worked in an unknown department (HR = 1.04, 95% CI = 1.01, 1.07) (**Table 12**). For each of the continuous models, those who worked in the unknown category (excluding the laborer department) also experienced a slightly elevated risk of COPD mortality reflecting a 4% increased risk of death for each year of work in an unknown department (HR=1.04; 95%CI = 1.00, 1.07) (**Table 12**).

Table 12. Risk of Chronic Obstructive Pulmonary Disease (COPD) Mortality[a] by Cumulative Employment Duration (in years)

Cumulative Employment Duration (in years)	Hazards Ratio	95% CI
By Departments		
Concentrating	1.00	0.94, 1.07
Crushing	0.99	0.90, 1.10
Mining	1.01	0.98, 1.03
Office/Control Room	0.99	0.96, 1.03
Pelletizing	0.99	0.95, 1.04
Shop Mobile	0.97	0.95, 1.00
Shop Station	0.97	0.93, 1.01
Ore Dressing	0.32	0.04, 2.40
Laborer	1.06	0.97, 1.15
Unknown	1.04	1.00, 1.07
Hematite	1.02	0.99, 1.04
By Industry[b]		
Taconite	0.99	0.98, 1.01
Hematite	1.03	1.00, 1.05
By Production Departments		
Production	1.00	0.98, 1.02
Non-Production	0.98	0.96, 1.00
Laborer & Unknown[c]	1.04	1.01, 1.07
Hematite	1.02	0.99, 1.04

[a]Cases are defined by COPD as an underlying cause of death
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive
[c]Unknown includes any individual who did not have a definitive job title or department as well as any workers who were in laborer department

Utilizing categorical variables, the current study did not identify a pattern of increased COPD underlying mortality based on quartiles of the cumulative years of employment in taconite, nor based on quartiles of the cumulative years of employment in production departments (**Table 13**).

Table 13. Risk of Chronic Obstructive Pulmonary Disease (COPD) Mortality[a] by Quartiles of Cumulative Employment Duration (in years)

	Hazards Ratio	95% CI
Quartiles of Cumulative Employment Duration in Taconite[b]		
Taconite Q1 (ref)		
Taconite Q2	1.07	0.71, 1.64
Taconite Q3	1.09	0.71, 1.66
Taconite Q4	0.95	0.61, 1.46
Hematite Only	0.98	0.64, 1.49
Quartiles of Cumulative Employment Duration in Production Departments[c]		
Production Q1 (ref)		
Production Q2	0.96	0.57, 1.62
Production Q3	1.53	0.89, 2.63
Production Q4	1.11	0.64, 1.90
Non-Production	1.08	0.69, 1.69
Hematite Only	1.07	0.66, 1.72

[a]Cases are defined by COPD as an underlying cause of death
[b]Minimum and maximum values for quartiles of cumulative employment duration in taconite (in years) are as follows: Q1=(0.003, 2.086); Q2=(2.103, 7.836); Q3=(7.866, 21.084); Q4=(21.123, 47.039)
[c]Minimum and maximum values for quartiles of cumulative employment duration in production departments (in years) are as follows: Q1= (0.003, 0.917); Q2=(0.964, 3.619); Q3=(3.671, 8.906); Q4=(9.150, 37.895)

For each of the analyses of employment duration, the estimates and confidence intervals found using COPD underlying versus COPD underlying/contributing were similar in magnitude and direction and the confidence intervals continued to include the null value (**Supplemental Table 11**). However, the association identified between cumulative years of employment in an unknown department (excluding those in the laborer department) was no longer present when underlying and contributing mortality due to COPD was used (HR=1.00; 95%CI=0.97, 1.03). Additionally, the association between cumulative years of employment in hematite and mortality due to underlying and contributing COPD remained the same, but the confidence interval no longer included the null value (HR=1.02; 1.00, 1.04).

While there were differences in the distribution of quartiles for COPD underlying and COPD underlying/contributing (**Supplemental Table 9**), and the estimates and the confidence intervals found for COPD underlying and COPD underlying/contributing in the categorical models differed in magnitude in some instances (**Supplemental Table 12**), the associations remained non-significant (i.e., the 95%CI included the null value).

Respirable Dust

Cumulative respirable dust exposure (in mg/m^3*years) was not associated with increased risk of death due to COPD among taconite workers (COPD underlying: HR = 0.98; 95% CI = 0.93, 1.04) (**Table 14**). When investigating quartiles of respirable dust exposure, increasing quartiles of exposure, as compared to the first quartile, did not indicate an increased risk of death due to COPD (**Table 15**).

Table 14. Risk of Chronic Obstructive Pulmonary Disease (COPD) Mortality[a] by Cumulative Exposure to Respirable Dust and Respirable Silica

Cumulative Exposure ((mg/m^3)*years)	Hazards Ratio	95% CI
Respirable Dust (RD)	0.98	0.93, 1.04
Respirable Silica	0.82	0.51, 1.31

[a]Cases are defined by COPD as an underlying cause of death

Table 15. Risk of Chronic Obstructive Pulmonary Disease (COPD) Mortality[a] by Quartiles of Cumulative Exposure to Respirable Dust and Respirable Silica (in mg/m^3*years)

Quartiles of Cumulative Respirable Dust Exposure[b]	Hazards Ratio	95% CI
RD Q1 (ref)		
RD Q2	0.80	0.52, 1.23
RD Q3	1.00	0.65, 1.54
RD Q4	0.73	0.47, 1.14
Hematite Only	0.82	0.54, 1.26
Quartiles of Cumulative Respirable Silica Exposure[c]		
RS Q1 (ref)		
RS Q2	0.85	0.56, 1.29
RS Q3	0.96	0.63, 1.46
RS Q4	0.74	0.48, 1.14
Hematite Only	0.83	0.55, 1.26

[a]Cases are defined by COPD as an underlying cause of death
[b]Minimum and maximum values for quartiles of cumulative respirable dust (in mg/m^3*years) are as follows: Q1= (0.004, 0.412); Q2=(0.412, 1.608); Q3=(1.616, 3.522); Q4=(3.533, 14.531)
[c]Minimum and maximum values for quartiles of cumulative respirable silica (in mg/m^3*years) are as follows: Q1=(0.000, 0.0.49); Q2=(0.049, 0.185); Q3=(0.185, 0.410); Q4=(0.412, 1.705)

Further, although the estimates slightly differed between COPD underlying and COPD underlying/contributing, increasing quartiles of respirable dust did not demonstrate a pattern of increasing mortality due to COPD underlying/contributing and the 95% confidence intervals for the estimates included the null value (**Supplemental Table 11 and Supplemental Table 12**).

<u>*Respirable Silica*</u>

Increases in cumulative respirable silica exposure (in mg/m^3*years) per year did not confer an increased risk of death due to COPD among taconite workers (HR = 0.82, 95% CI = 0.51, 1.31) (**Table 14**). No pattern was observed for increases in quartiles of silica exposure in relation to risk of death due to COPD, and the 95% confidence intervals fo the estimates included the null value (**Table 15**). The estimates and confidence intervals found for COPD underlying and COPD underlying/contributing were similar and followed similar patterns (i.e., the estimates remained in the same direction and the 95% confidence intervals included the null value) (**Supplemental Table 11 and Supplemental Table 12**).

Discussion

Previous studies have reported an association between workplace exposures and COPD outcomes including respirable dust and respirable silica (70-77). However, similar to Allen *et al.* (6), the findings of the current study do not indicate an increased risk of death due to COPD based on duration of employment in taconite operations in Minnesota. An association was observed between COPD and having a history of work in an unknown department or production category, but these associations are difficult to interpret. Moreover, the associations disappeared when both COPD based on underlying and contributing causes were taken into consideration. Some evidence of associations between COPD, both underlying and contributing cases combined, and employment in the hematite mines was observed. However, each of the associations with hematite included the null value as the lower bound of the 95% confidence interval. Lastly, no associations were found between respirable dust or respirable silica with COPD mortality.

In general, previous studies have linked workplace exposures to COPD outcomes (72, 77, 78) (**Supplemental Table 13**). Bakke *et al.* investigated workplace exposures among a Norwegian population using population-based questionnaires that included questions related to smoking habits and occupational exposure to dust or gas, and respiratory disorders (78). Participants' longest job held and current occupation were used to assign exposure based on occupation. Each occupation was categorized into three categories including no airborne exposure (e.g, teachers, fishermen, clerks, and taxi drivers), moderate degree of airborne exposure (e.g., farmers, greasers, weavers, and typographers), and high degree of airborne exposure (e.g., foundry workers, painters, and insulation workers). Airborne exposures included dusts, fumes, mists, and gases. Chronic obstructive lung disease and asthma were found to be elevated among those with occupations having the highest degree of airborne exposure compared to those without airborne exposures after adjusting for sex, age, and smoking (present occupation: OR=3.6; 95%CI=1.3, 9.9; longest held occupation: OR=2.5; 95%CI=1.1, 5.9). Further, based on analyses adjusting for sex, age and smoking, an association was found between exposure to quartz dust and obstructive lung disease (OR=2.3; 95%CI=1.3, 6.0). However, given that no exposure measurements were taken and airborne exposure was only determined qualitatively based on occupational titles, there is likely a high degree of exposure misclassification that took place in this study. Similarly, although participants filled out a questionnaire related to occupational exposures to determine exposure to quartz dust, no exposure measurements were taken to determine exposure to quartz and quartz exposure was solely based on self-report which also likely resulted in exposure misclassification.

Weinmann *et al.* conducted a case-control study among members of Kaiser Permanente Northwest health maintenance organization (HMO) in Portland, Oregon aged 45 years and older (77). Study participants were stratified by smoking status based on the electronic health record. COPD was determined based on the medical record. Controls were frequency matched 1:1 to cases based on age, sex, and smoking status. However, after recruitment only 388 COPD cases and 356 controls were included in the final study. Based on occupational information collected via interview, industrial hygienists assigned a score for potential exposure related to mineral dusts, metal dusts and fumes, organic dusts, irritant gases or vapors, sensitizers, organic solvents, diesel exhaust, and environmental tobaccos smoke. The industrial hygienists also assigned overall scores to each occupation. COPD was determined to be associated with exposure to any dust, irritant gases or vapors, sensitizers, organic solvents, or diesel exhaust exposure after adjusting for age, sex, ever-smoking, and pack-years (OR=1.5; 95%CI=1.1, 2.1). Similar to Bakke *et al.*, given that no exposure measurements were taken for any of these exposures, exposure misclassification was likely (77, 78). Further, the qualitative exposure metrics used combined dust along with other potential exposures, and as a result, it is possible that these associations may have been driven by exposures other than solely respirable dust.

Blanc *et al.* also conducted a case-control study among Kaiser Permanente Medical Care Program members (72). Occupational risk was determined using a job-exposure matrix that categorized occupations as low, intermediate, and high probability of exposure. For example, occupations with a high probability of exposure included truck and heavy equipment operators as well as most construction jobs. The authors found that the odds of COPD were increased among those with a high probability of occupational exposure after adjusting for age, sex, race, and smoking (OR=2.27; 95%CI=1.46, 3.52). As with Bakke *et al.* and Weinmann *et al.*, no exposure metrics were used and exposure assessment was based solely on qualitatively assigning occupations to low, intermediate, and high probabilities of exposure (72, 77, 78).

More recent studies have identified associations specifically between respirable dust and respirable silica with COPD outcomes (75, 79). Among a cohort of men from the British Pneumoconiosis Field Research (PFR) program, Miller *et al.* investigated various mortality outcomes associated with respirable dust and silica (79). The authors found increased death due to COPD among the cohort in comparison to expected deaths based on the regional reference population between 1959 and 2005 (SMR=115.5; 95%CI=108.0, 123.6). Generally, Miller *et al.* found that the average cumulative respirable dust across surveys was approximately 139 $g.h.m^{-3}$ (approximately 30 years of 1740 working hours in a mean concentration of 2.65 (mg/m^3)*years) and the average cumulative respirable silica was 6.5 $g.h.m^{-3}$ (approximately 30 years of 1740 working hours in a mean concentration of 0.12 (mg/m^3)*years). The authors determined that after adjusting for entry date, age (quadratic) X (smoking at entry), cigarette use at entry into the cohort and regional rates, the risk of COPD mortality was increased among those with dust exposure before accounting for a lag (HR=1.14; 95%CI=1.08, 1.20) and after a 15-year lag (HR =1.17; 95%CI=1.11, 1.24). Similar results were found for quartz exposure without a lag (HR =1.08; 95%CI=1.03, 1.13) and after a 15-year lag (HR =1.11; 95%CI=1.05, 1.16). When both lagged exposures of quartz and dust were accounted for in the model, only the exposure to dust indicated an increased risk of

COPD mortality (quartz: HR =0.96; 95%CI=0.88, 1.04; dust: HR =1.21; 95%CI=1.11, 1.32). Although Miller *et al.* used quantitative exposure metrics and the cumulative respirable dust and silica measurements in the Miller *et al.* study were similar to those in the current study, the increased risk of COPD due to respirable dust and respirable silica, respectively, were based on comparisons to regional rates rather than another working group or an internal comparison (79). Further, when the authors adjusted for both respirable dust and respirable silica only respirable dust remained significant which indicates the possibility that respirable silica may not be associated increased COPD mortality (79). Lastly, while Miller *et al.* found an association between respirable dust and COPD mortality, respirable dust may contain a variety of constituents that differ by industry and the constituents of respirable dust found in the PFR program likely differ from those found in taconite mining (79).

In a recent study, Lenander-Ramirez *et al.* evaluated morbidity and mortality due to various diseases, including COPD, in relation to respirable silica among a cohort of Swedish iron foundry workers (75). The authors found significantly increased SIRs for all exposure groups of respirable dust (≤2.76, 2.77-9.82, 9.83+ (mg/m^3)*years) as well as for all exposure groups of respirable silica (≤0.14, 0.15-0.38, 0.39+ (mg/m^3)*years). However, for the SMRs, significant associations were only identified for the highest tertile of respirable silica exposure for respiratory diseases (0.39+ (mg/m^3)*years: SMR=1.80; 95%CI=1.08, 2.81). For SMRs related to respirable dust exposure, no significant associations were found. Similar to Miller *et al.* and unlike the current study, Lenander-Ramirez *et al.* utilized a general population as a comparison group (75, 79). Further, while it is possible that respirable dust and silica, respectively, may lead to COPD incidence, COPD may be reversible, and as a result associations between COPD incidence and mortality may differ (46).

While the current study's results differed from previous studies' findings, there are a number of risk factors that were not accounted for in this study that could contribute to COPD in this population. For example, smoking, genetics, and a history of respiratory infections are all risk factors for COPD (22, 46, 67). While these risk factors could not be accounted for in the current study, including these factors would likely attenuate the relationship between employment duration and respirable exposures with COPD mortality. Allen *et al.* previously estimated the association between smoking and EMP as well as silica exposure among taconite workers who participated in the 2010 Taconite Workers Health study (4). The authors determined that 'ever' smokers had higher cumulative exposures than 'never' smokers for EMPs (3.3 vs. 2.5 (EMP/cc)*years, respectively) and silica (0.5 vs. 0.4 silica (mg/m^3)*years, respectively). The difference in exposure among 'ever' versus 'never' smokers with 'ever' smokers experiencing higher exposures than 'never' smokers suggests that the current analyses may overestimate the association between respirable dust and respirable silica with COPD (80). However, without information related to these risk factors including smoking, genetics, and respiratory infection history specifically among the taconite workers in the current study, the direction of the bias is unknown.

Although the current study does not suggest an association between respirable dust or silica with COPD, there were limitations. While exposure estimates for respirable dust and respirable silica were reconstructed using available historical data and personal sampling data, exposure data was not collected for all SEGs and gaps in historical exposure data existed (3, 12). To reconstruct historical data, a regression model and imputation were used and a linear trend in historical exposure was assumed (12). Additionally, Shao *et al.* assumed that the historical exposures were based on random sampling and not worst-case sampling, which may have led to an over- or under-estimate depending on how historical samples were measured (12). Also, Shao *et al.* assumed that respirable silica was a certain percentage of taconite ore and that the percentage of silica contained in the ore did not change over time by mine or department which may have also led to potential exposure misclassification (12). Although there was incomplete exposure data and an assumption of a historical linear trend among others, Shao *et al.* had a substantial number of historical and current samples that provided highly informative respirable dust estimates. Additionally, the estimated exposures found by Shao *et al.* used in the current study resulted in exposures that were comparable to respirable dust and silica exposures found in the Lenander-Ramirez *et al.* study and the Miller *et al.* study (12, 75, 79).

It is also possible that misclassification of job titles may have also occurred. Although work history records were standardized to the extent possible, job titles within the employment record were often incomplete or difficult to interpret. As a result, it is possible that job titles were assigned to the incorrect SEG, and therefore the incorrect department resulting in employment duration and exposure misclassification. The direction of bias from this misclassification is not known.

Despite the limitations of the exposure data in the current study, employment duration data are less likely to be biased and may serve as a proxy for exposures that are present within taconite mining, including exposures related to respirable dust and respirable silica, among others. However, results between employment duration and COPD mortality were similar to those using exposure data in the current study, i.e., there was little evidence of an association between employment duration and COPD mortality.

In a study among a similar group of taconite workers, Allen *et al.* determined that smoking status differed based on exposure status and it is likely that in the current study that may be the case as well (4). Specifically, more exposed workers may be more likely to smoke than those who experienced less exposure and given the time period, smoking was also more prevalent. Although it is possible that, had smoking been accounted for, it would have driven the estimate toward the null. However, the actual direction of the bias in the current study is unknown since smoking history was not ascertained for the current study's participants.

In general, the current study did not identify an association between taconite worker exposures with COPD mortality. One potential reason for this may be due to the healthy hire effect. That is, individuals who were placed in jobs that were more highly exposed were healthier than those who were placed in lower exposure jobs; therefore, there may not be an association among highly exposed individuals since they were already at lower risk for COPD mortality. Despite lack of information on health history, there was information on department, and no significant differences in the associations were observed by department indicating that it is possible that the healthy hire effect did not impact the results of this study. Another possible explanation is that taconite workers, on average, were employed for less than 10 years and the duration of employment was not substantial enough to elicit adverse health effects. However, given that associations between respirable dust and respirable silica were considered and no association was found, it remains unlikely that exposures experienced in taconite contribute to COPD mortality.

Another possible explanation for the lack of association is due to COPD not being identified as a primary cause of death or even being mentioned on the death certificate at all. In general, COPD is often undiagnosed which is one factor that contributes to the absence of COPD on the death certificate (31, 81, 82). Further, individuals with a documented diagnosis of COPD often do not have COPD listed on the death certificate (28, 29). Drummond *et al.* found that only up to approximately 58% of those diagnosed with COPD have COPD listed on the death certificate as a primary or contributing cause (29). Lindberg *et al.* found similar results with COPD being listed only on 57.1% the death certificates among those with a previously identified severe or very severe diagnosis of COPD (32). Even among those whose death was related to a COPD exacerbation, Drummond *et al.* only 34% had COPD listed as a primary cause of death and COPD was not mentioned at all on 21% of these deaths (32). Berry and Wise also found that for those with a diagnosis of COPD, those with mild or moderate COPD often had cardiovascular disease or malignancy listed as the predominant cause of death (28). Given that COPD is often not captured as the primary cause of death when COPD is reported on the death certificate, the current study extended the definition of COPD mortality to include underlying and contributing causes of death due to COPD to rectify any possible underreporting that occurred. While this approach cannot account for COPD cases that were not listed at all on the death certificate or those that may have been listed as contributing causes for primary causes of death other than IHD, it does provide a more comprehensive estimate of the mortality burden due to COPD.

The current study also had several strengths. This is the first study to investigate the relationship between respirable dust and respirable silica with COPD mortality using a quantitative exposure assessment approach within this taconite cohort. Additionally, this is the first study to investigate the potential misclassification of COPD on the death certificate regarding IHD as a primary cause of death. Although there are occupational studies that have investigated the association between occupations and COPD generally as well as a few that have investigated the association between respirable dust and silica with COPD, this is the first study to investigate the association among taconite miners. Although studies involving respirable silica may be more generalizable across study populations, the various constituents present in respirable dust may differ across industries. As a result, unlike other occupational studies that do not focus on taconite mining specifically, the current study provides insight into the potential effects of cumulative exposure to respirable dust over an individual's entire work history in the taconite industry. Further, although some previous studies identified an association between respirable silica and COPD, these studies compared regional or national rates of COPD to the working population which may have resulted in a healthy worker survival bias effect (75, 79). However, using a nested case-control design, in which cases and controls arose from the same working population, the current study provides evidence that there is likely not an association between respirable silica and COPD.

When underlying causes of death are due to chronic diseases that may have comorbidities, utilizing the contributing cause of death may provide additional insight into the effect of taconite work on COPD mortality (33). Although misclassification of the underlying cause of death is possible when chronic diseases such as COPD and IHD are comorbidities, given the similarity of results between COPD underlying and COPD underlying/contributing, there is little evidence of misclassification of COPD within the current cohort.

Further, the study sample was large and as a result the estimates were generally precise when estimating the effects of exposures associated with IHD mortality. Lastly, despite the difficulties with work history abstractions and job titles, relying on work histories to define worker's exposure eliminates the potential for recall bias if instead workers or their families had been questioned about their roles in taconite mining.

Conclusion

The current study evaluated did not identify associations between COPD mortality and employment duration, respirable dust or respirable silica-exposures within taconite mining. Although, taconite miners experience unique exposures to respirable dust and respirable silica that often occur at higher levels than the general population, the findings of this study suggest that occupational factors associated with taconite mining are unlikely to lead to increased COPD mortality in this group of miners.

Chapter 5: Conclusion

Summary

Manuscript 1 (Chapter 2) evaluated whether underlying causes of death due to COPD and IHD were under- or over-estimated, respectively, among taconite workers using a multiple cause of death analysis. A population of 30,779 taconite workers were included in the study and compared to the general Minnesota population between 1970 to 2010. Of deceased taconite workers 2,127 had IHD as an underlying cause of death and 560 had IHD listed as a contributing case of death. For COPD, 361 workers had COPD listed as the underlying cause of death with an additional 490 identified based on the contributing cause of death.

The SMRs for the underlying cause of death were 1.04 (95% CI = 1.00, 1.09) for IHD and 0.85 (95% CI = 0.76, 0.94) for COPD. For an underlying or contributing cause of death due to IHD, the SMR was 1.01 (95% CI = 0.98, 1.05) whereas for COPD the SMR was 0.90 (95% CI = 0.84, 0.97). The results from this manuscript indicated that mortality due to IHD or COPD among taconite workers as compared to the general Minnesota population was not elevated based on use of underlying cause of death alone, nor based on the combination of underlying and contributing causes of death. Further, the direction of the estimates found for IHD and COPD mortality did not differ from previous studies investigating IHD and COPD mortality using solely the underlying cause of death. Although increased mortality was not identified, *Manuscripts 2 and 3* evaluated whether taconite exposures had an impact on associations with IHD or COPD mortality, respectively. Further, sensitivity analyses extending the definition of IHD and COPD mortality to include contributing causes of death were also explored in *Manuscripts 2 and 3*, respectively.

Manuscripts 2 (Chapter 3) and 3 (Chapter 4) explored associations between employment duration, respirable dust, and respirable silica among a cohort of Minnesota taconite miners with IHD and COPD mortality, respectively. Further, for Manuscript 2, a secondary analysis was conducted to determine the impact of potential misclassification of IHD as the underlying cause of death due to comorbidities such as COPD. For Manuscript 3, a secondary analysis was also conducted to determine the impact of potential misclassification of COPD as the underlying cause of death due to comorbidities such as IHD. Manuscripts 2 and 3 used a nested case-control design within a cohort of 31,067 taconite workers with cases vital statuses identified through 2010.

For *Manuscript 2*, a total of 2185 causes of death due to IHD as an underlying cause of death were identified with a total of 2217 deaths due to IHD when contributing causes were considered. No associations with IHD mortality were identified for employment duration by department, industry, or production departments. Additionally, no association was found between respirable dust (HR=0.99; 95%CI=0.97, 1.02) or respirable silica (HR=1.02; 95%CI=0.84, 1.24) with IHD as an underlying cause of death indicating that inclusion of contributing causes of death due to IHD resulted in associations that were essentially unchanged from those identified by IHD as an underlying cause of death only.

For *Manuscript 3*, a total of 363 causes of death due to COPD as an underlying cause were identified with a total of 499 deaths when contributing causes of death due to COPD were considered. No associations with COPD mortality were identified for employment duration by department or industry. An association was found by production departments for individuals with unknown work history and laborers (HR=1.04; 95%CI=1.01, 1.07); however, the association was no longer significant when contributing causes of death due to COPD were included (HR=1.01; 95%CI=0.98, 1.03). No association was found between respirable dust (HR=0.98; 95%CI=0.93, 1.04) or respirable silica (HR=0.82; 95%CI=0.51, 1.31) with COPD as an underlying cause of death. Results that included contributing causes of death due to COPD with IHD listed as a primary cause of death were essentially unchanged from those with COPD as an underlying cause of death only.

Overall Conclusions

Overall, the results suggest that extending the cause of death to include contributing causes of death for COPD or IHD mortality, respectively, did not change the conclusions from previous studies (i.e., the magnitude and direction of the associations remained the same). Further, our results indicate that occupational exposures experienced by taconite workers are unlikely to contribute to increased mortality due to COPD or IHD.

This study was the first to explore the impact of including contributing causes of death for mortality due to IHD and COPD. This was also the first study to evaluate the association between taconite exposures including duration of employment, respirable dust, and respirable silica on IHD and COPD mortality, respectively, among this cohort of taconite workers. These studies build upon the existing understanding of exposures that impact the health of taconite miners in Minnesota and provide a broader understanding of health risks that taconite miners experience. In light of the limitations, these studies indicate that occupational exposures in taconite mining are unlikely to contribute to increased IHD or COPD mortality among this cohort of taconite miners.

References

1. Minnesota Department of Natural Resources. Mining in Minnesota: What's mined in Minnesota? [Available from: https://www.dnr.state.mn.us/education/geology/digging/mining.html.

2. Berndt ME, Brice WC. The origins of public concern with taconite and human health: Reserve Mining and the asbestos case. Regulatory Toxicology and Pharmacology. 2008;52(1, Supplement):S31-S9.

3. Hwang J, Ramachandran G, Raynor PC, Alexander BH, Mandel JH. A comprehensive assessment of exposures to respirable dust and silica in the taconite mining industry. Journal of occupational and environmental hygiene. 2017;14(5):377-88.

4. Allen EM, Alexander BH, MacLehose RF, Nelson HH, Ramachandran G, Mandel JH. Cancer incidence among Minnesota taconite mining industry workers. Annals of epidemiology. 2015;25(11):811-5.

5. Allen EM, Alexander BH, MacLehose RF, Nelson HH, Ryan AD, Ramachandran G, et al. Occupational exposures and lung cancer risk among Minnesota taconite mining workers. Occupational and environmental medicine. 2015;72(9):633-9.

6. Allen EM, Alexander BH, MacLehose RF, Ramachandran G, Mandel JH. Mortality experience among Minnesota taconite mining industry workers. Occupational and environmental medicine. 2014;71(11):744-9.

7. Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. Journal of occupational medicine : official publication of the Industrial Medical Association. 1988;30(6):506-11.

8. Cooper WC, Wong O, Trent LS, Harris F. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. Journal of occupational medicine : official publication of the Industrial Medical Association. 1992;34(12):1173-80.

9. Lambert CS, Alexander BH, Ramachandran G, MacLehose RF, Nelson HH, Ryan AD, et al. A case-control study of mesothelioma in Minnesota iron ore (taconite) miners. Occupational and environmental medicine. 2016;73(2):103-9.

10. Minnesota Department of Health. Mesothelioma in Northeastern Minnesota and Two Occupational Cohorts: 2007 Update. 2007.

11. Hwang J, Ramachandran G, Raynor PC, Alexander BH, Mandel JH. Comprehensive assessment of exposures to elongate mineral particles in the taconite mining industry. The Annals of occupational hygiene. 2013;57(8):966-78.

12. Shao Y, Hwang J, MacLehose RF, Alexander BH, Mandel JH, Raynor PC, et al. Reconstructing Historical Exposures to Respirable Dust and Respirable Silica in the Taconite Mining Industry for 1955-2010. Annals of work exposures and health. 2022;66(4):459-71.

13. American Conference of Governmental Industrial Hygienists (ACGIH). Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs). 2023.

14. Dockery DW, Pope CA, 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. The New England journal of medicine. 1993;329(24):1753-9.

15. Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation. 2004;109(1):71-7.

16. Neophytou AM, Noth EM, Liu S, Costello S, Hammond SK, Cullen MR, et al. Ischemic Heart Disease Incidence in Relation to Fine versus Total Particulate Matter Exposure in a U.S. Aluminum Industry Cohort. PloS one. 2016;11(6):e0156613.

17. Chen W, Liu Y, Wang H, Hnizdo E, Sun Y, Su L, et al. Long-term exposure to silica dust and risk of total and cause-specific mortality in Chinese workers: a cohort study. PLoS medicine. 2012;9(4):e1001206.

18. Lee MS, Eum KD, Fang SC, Rodrigues EG, Modest GA, Christiani DC. Oxidative stress and systemic inflammation as modifiers of cardiac autonomic responses to particulate air pollution. International journal of cardiology. 2014;176(1):166-70.

19. Gurgueira SA, Lawrence J, Coull B, Murthy GG, González-Flecha B. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environmental health perspectives. 2002;110(8):749-55.

20. Brook RD. Cardiovascular effects of air pollution. Clinical science (London, England : 1979). 2008;115(6):175-87.

21. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. Ann N Y Acad Sci. 2015;1340:84-94.(doi):10.1111/nyas.12720. Epub 2015 Feb 25.

22. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379(9823):1341-51.

23. Scott J. Pathophysiology and biochemistry of cardiovascular disease. Current opinion in genetics & development. 2004;14(3):271-9.

24. Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet. 2016;388(10045):696-704.

25. Huynh T, Ramachandran G, Quick H, Hwang J, Raynor PC, Alexander BH, et al. Ambient Fine Aerosol Concentrations in Multiple Metrics in Taconite Mining Operations. Annals of work exposures and health. 2019;63(1):77-90.

26. Toren K, Jarvholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. Chest. 2014;145(5):992-7.

27. Hwang J, Ramachandran G, Raynor PC, Alexander BH, Mandel JH. The relationship between various exposure metrics for elongate mineral particles (EMP) in the taconite mining and processing industry. Journal of occupational and environmental hygiene. 2014;11(9):613-24.

28. Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. Copd. 2010;7(5):375-82.

29. Drummond MB, Wise RA, John M, Zvarich MT, McGarvey LP. Accuracy of death certificates in COPD: analysis from the TORCH trial. Copd. 2010;7(3):179-85.

30. Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. Eur Respir J. 2006;28(4):781-5.

31. Lindberg A, Bjerg A, Rönmark E, Larsson LG, Lundbäck B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med. 2006;100(2):264-72.

32. Lindberg A, Lindberg L, Sawalha S, Nilsson U, Stridsman C, Lundbäck B, et al. Large underreporting of COPD as cause of death-results from a population-based cohort study. Respir Med. 2021;186:106518.

33. Steenland K, Nowlin S, Ryan B, Adams S. Use of multiple-cause mortality data in epidemiologic analyses: US rate and proportion files developed by the National Institute for Occupational Safety and Health and the National Cancer Institute. American journal of epidemiology. 1992;136(7):855-62.

34. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. An analysis using multiple-cause mortality data. Am J Respir Crit Care Med. 1997;156(3 Pt 1):814-8.

35. Kircher T, Anderson RE. Cause of death. Proper completion of the death certificate. Jama. 1987;258(3):349-52.

36. US Census Bureau. State Intercensal Tables: 1970-1979; 1970-1979 Population Estimates by Age, Sex, and Race, PE-19 [Available from: https://www.census.gov/data/tables/time-series/demo/popest/1970s-state.html

37. US Census Bureau. County Intercensal Tables: 1980-1989; Intercensal County Estimates by Age, Sex, Race: 1980-1989 [Available from: https://www.census.gov/data/tables/time-series/demo/popest/1980s-county.html.

38. US Census Bureau. State and County Intercensal Datasets: 1990-2000; Intercensal State and County Characteristics Population Estimates with 1990-Base Race Groups [Available from: https://www.census.gov/data/datasets/time-series/demo/popest/intercensal-1990-2000-state-and-county-characteristics.html.

39. US Census Bureau. State Intercensal Datasets: 2000-2010; Intercensal Estimates of the Resident Population by Five-year Age Groups, Sex, Race and Hispanic Origin for States and the United States: April 1, 2000 to July 1, 2010 [Available from: https://www.census.gov/data/datasets/time-series/demo/popest/intercensal-2000-2010-state.html.

40. Minnesota Center for Health Statistics. Minnesota Department of Health [Available from: https://www.health.state.mn.us/data/mchs/index.html.

41. The National Institute for Occupational Safety and Health (NIOSH). UCOD 119 Mapping File 2008 [Available from: https://www.cdc.gov/niosh/ltas/rates.html.

42. The National Institute for Occupational Safety and Health (NIOSH). Life Table Analysis System (LTAS) [Available from: https://www.cdc.gov/niosh/ltas/.

43. Yoon J, Chow A. Comparing chronic condition rates using ICD-9 and ICD-10 in VA patients FY2014-2016. BMC Health Serv Res. 2017;17(1):572.

44. Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology. Second ed. New York, New York: Oxford University Press; 2004.

45. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. Hyattsville, MD: National Center for Health Statistics; 2018.

46. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson L, Loscalzo J. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw Hill Education; 2015.

47. Institute of Medicine (US) Committee on Social Security Cardiovascular Disability Criteria. Cardiovascular Disability: Updating the Social Security Listings. Washington (DC): National Academies Press (US); 2010.

48. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Translational research : the journal of laboratory and clinical medicine. 2013;162(4):237-51.

49. Iron Mining Association of Minnesota. Minnesota Iron Mining [Available from: https://www.taconite.org/mining-industry.

50. Ostro B, Lipsett M, Reynolds P, Goldberg D, Hertz A, Garcia C, et al. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. Environmental health perspectives. 2010;118(3):363-9.

51. Costello S, Attfield MD, Lubin JH, Neophytou AM, Blair A, Brown DM, et al. Ischemic Heart Disease Mortality and Diesel Exhaust and Respirable Dust Exposure in the Diesel Exhaust in Miners Study. American journal of epidemiology. 2018;187(12):2623-32.

52. University of Minnesota School of Public Health. Taconite Workers Health Study: Final Report to the Minnesota Legislature. 2015.

53. Monson Geerts SD, Hudak G, Marple V, Lundgren D, Zanko L, Olson B. Minnesota Taconite Workers Health Study: Environmental Study of Airborne Particulate Matter in Mesabi Iron Range Communities and Taconite Processing Plants - Mesabi Iron Range Community Particulate Matter Collection and Gravimetric Analysis. University of Minnesota Digital Conservancy: University of Minnesota Duluth; 2019.

54. Ljungman PLS, Andersson N, Stockfelt L, Andersson EM, Nilsson Sommar J, Eneroth K, et al. Long-Term Exposure to Particulate Air Pollution, Black Carbon, and Their Source Components in Relation to Ischemic Heart Disease and Stroke. Environmental health perspectives. 2019;127(10):107012.

55. Rodins V, Lucht S, Ohlwein S, Hennig F, Soppa V, Erbel R, et al. Long-term exposure to ambient source-specific particulate matter and its components and incidence of cardiovascular events - The Heinz Nixdorf Recall study. Environ Int. 2020;142:105854.

56. Thurston GD, Burnett RT, Turner MC, Shi Y, Krewski D, Lall R, et al. Ischemic Heart Disease Mortality and Long-Term Exposure to Source-Related Components of U.S. Fine Particle Air Pollution. Environmental health perspectives. 2016;124(6):785-94.

57. Monson Geerts SD, Hudak G, Marple V, Lundren D, Gordee S, Olson B, et al. Minnesota Taconite Workers Health Study: Environmental Study of Airborne Particulate Matter in the Mesabi Iron Range Communities and Taconite Processing Plants - Elemental Chemistry of Particulate Matter. . Natural Resources Research Institute: University of Minnesota Duluth; 2019. Contract No.: NRRI/RI-2019/32.

58. Shao Y. Respiratory Diseases and Exposures to Taconite Dust Components. University of Minnesota Digital Conservancy (2018).

59. Costello S, Garcia E, Hammond SK, Eisen EA. Ischemic heart disease mortality and PM(3.5) in a cohort of autoworkers. American journal of industrial medicine. 2013;56(3):317-25.

60. Neophytou AM, Costello S, Brown DM, Picciotto S, Noth EM, Hammond SK, et al. Marginal structural models in occupational epidemiology: application in a study of ischemic heart disease incidence and PM2.5 in the US aluminum industry. American journal of epidemiology. 2014;180(6):608-15.

61. Porter DW, Hubbs AF, Mercer R, Robinson VA, Ramsey D, McLaurin J, et al. Progression of lung inflammation and damage in rats after cessation of silica inhalation. Toxicol Sci. 2004;79(2):370-80.

62. Du Z, Zhao D, Jing L, Cui G, Jin M, Li Y, et al. Cardiovascular toxicity of different sizes amorphous silica nanoparticles in rats after intratracheal instillation. Cardiovasc Toxicol. 2013;13(3):194-207.

63. Lai H, Liu Y, Zhou M, Shi T, Zhou Y, Weng S, et al. Combined effect of silica dust exposure and cigarette smoking on total and cause-specific mortality in iron miners: a cohort study. Environ Health. 2018;17(1):46.

64. Wang D, Yang M, Liu Y, Ma J, Shi T, Chen W. Association of Silica Dust Exposure and Cigarette Smoking With Mortality Among Mine and Pottery Workers in China. JAMA Netw Open. 2020;3(4):e202787.

65. Wang X, Li G, Liu L, Westerdahl D, Jin X, Pan X. Effects of Extreme Temperatures on Cause-Specific Cardiovascular Mortality in China. Int J Environ Res Public Health. 2015;12(12):16136-56.

66. Davies HW, Teschke K, Kennedy SM, Hodgson MR, Hertzman C, Demers PA. Occupational exposure to noise and mortality from acute myocardial infarction. Epidemiology. 2005;16(1):25-32.

67. Centers for Disease Control and Prevention (CDC). Chronic Obstructive Pulmonary Disease (COPD): Basics About COPD: CDC; 2021 [Available from: https://www.cdc.gov/copd/basics-about.html.

68. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018;12:1753465817750524.

69. Patel ARC, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. Chest. 2012;141(4):851-7.

70. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003;167(5):787-97.

71. Blanc PD. Occupation and COPD: a brief review. J Asthma. 2012;49(1):2-4.

72. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, et al. Occupational exposures and the risk of COPD: dusty trades revisited. Thorax. 2009;64(1):6-12.

73. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. J Occup Environ Med. 2008;50(3):366-70.

74. Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occupational and environmental medicine. 2003;60(4):237-43.

75. Lenander-Ramirez A, Bryngelsson IL, Vihlborg P, Westberg H, Andersson L. Respirable Dust and Silica: Respiratory Diseases Among Swedish Iron Foundry Workers. J Occup Environ Med. 2022;64(7):593-8.

76. Syamlal G, Doney B, Hendricks S, Mazurek JM. Chronic Obstructive Pulmonary Disease and U.S. Workers: Prevalence, Trends, and Attributable Cases Associated With Work. Am J Prev Med. 2021;61(3):e127-e37.

77. Weinmann S, Vollmer WM, Breen V, Heumann M, Hnizdo E, Villnave J, et al. COPD and occupational exposures: a case-control study. J Occup Environ Med. 2008;50(5):561-9.

78. Bakke PS, Baste V, Hanoa R, Gulsvik A. Prevalence of obstructive lung disease in a general population: relation to occupational title and exposure to some airborne agents. Thorax. 1991;46(12):863-70.

79. Miller BG, MacCalman L. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. Occupational and environmental medicine. 2010;67(4):270-6.

80. VanderWeele TJ, Hernán MA, Robins JM. Causal directed acyclic graphs and the direction of unmeasured confounding bias. Epidemiology. 2008;19(5):720-8.

81. Martinez CH, Mannino DM, Jaimes FA, Curtis JL, Han MK, Hansel NN, et al. Undiagnosed Obstructive Lung Disease in the United States. Associated Factors and Long-term Mortality. Ann Am Thorac Soc. 2015;12(12):1788-95.

82. Peña VS, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000;118(4):981-9.

Supplemental Tables

Supplemental Table 1. NIOSH-119 Table for Ischemic Heart Disease and Chronic Obstructive Pulmonary Disease ICD Codes, 1960-2004

	ICD Code Revision			
Disease	**Revision 7**	**Revision 8**	**Revision 9**	**Revision 10**
Ischemic Heart Disease	420	410-414	410-414, 429.2	I20#, I20.0-I20.1, I20.8-I20.9, I21#, I21.0-I21.4, I21.9, I22#, I22.0-I22.1, I22.8-I22.9, I24#, I24.1, I24.8-I24.9, I25#, I25.0-I25.6, I25.8-I25.9, I51.3, I51.6
Chronic Obstructive Pulmonary Disease	501-502, 527.1	490-492, 519.3	490-492, 496	J40#, J41#, J41.0-J41.1, J41.8, J42#, J43#, J43.0-J43.2, J43.8-J43.9, J44#, J44.0-J44.1, J44.8-J44.9

#: Indicates code with no decimal

Supplemental Table 2. Cumulative Employment Duration (in years) by Production Departments for IHD Underlying and IHD Underlying/Contributing

By Production Departments	IHD Underlying						IHD Underlying/Contributing					
	Cases			Controls			Cases			Controls		
	N	Mean (yrs)	SD	N	Mean (yrs)	SD	N	Mean (yrs)	SD	N	Mean (yrs)	SD
Production	1,129	7.48	8.42	2,000	7.48	8.58	1,143	7.51	8.47	2,019	7.49	8.64
Non-production	980	8.17	8.40	1,983	8.97	9.12	991	8.13	8.38	2,011	8.99	9.13
Hematite	1,336	5.31	7.00	2,507	4.55	6.08	1,358	5.35	7.05	2,552	4.55	6.06
Unknown	469	4.84	6.28	882	4.82	6.33	477	4.76	6.20	893	4.87	6.38

IHD=Ischemic Heart Disease

[a]Hematite includes any individual who worked within hematite (i.e., it is not mutually exclusive to the other departments)

[b]Unknown includes any individual who did not have a definitive job title or department (excludes laborer department)

Supplemental Table 3. Quartiles of Cumulative Employment Duration (in years) by Employment in the Taconite Industry and the Production Department and Exposure to Respirable Dust and Respirable Silica, Respectively (in mg/m^3*years) for IHD Underlying and IHD Underlying/Contributing

	IHD Underlying						IHD Underlying/Contributing					
	Cases			Controls			Cases			Controls		
Cumulative Employment Duration in Taconite[a,b]	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Q1	394	1.10	0.74	746	1.01	0.71	398	1.09	0.72	744	0.99	0.69
Q2	393	5.44	2.11	786	5.58	2.09	399	5.35	2.09	798	5.52	2.09
Q3	394	14.74	2.86	672	14.67	2.81	399	14.65	2.88	683	14.62	2.82
Q4	393	26.33	3.88	827	26.60	4.30	399	26.31	3.88	841	26.66	4.39
Cumulative Employment Duration in Production[c,d]												
Q1	284	0.41	0.28	530	0.41	0.27	286	0.41	0.28	536	0.41	0.27
Q2	281	2.05	0.70	456	2.05	0.73	286	2.05	0.70	462	2.05	0.73
Q3	282	7.13	2.43	526	6.78	2.29	286	7.13	2.44	531	6.81	2.31
Q4	282	20.37	5.61	488	20.98	5.55	285	20.49	5.64	490	21.10	5.72
Cumulative Exposure to Respirable Dust[e,f]												
Q1	394	0.32	0.17	761	0.30	0.17	399	0.32	0.17	767	0.30	0.17
Q2	393	1.20	0.38	757	1.23	0.39	399	1.19	0.38	765	1.23	0.39
Q3	394	2.94	0.57	738	2.86	0.55	399	2.94	0.57	746	2.86	0.56
Q4	393	5.76	1.75	775	5.96	1.84	398	5.78	1.75	788	5.97	1.86
Cumulative Exposure to Respirable Silica[g]												
Q1	407	0.03	0.02	807	0.03	0.02	412	0.03	0.02	812	0.03	0.02
Q2	389	0.14	0.05	798	0.15	0.05	394	0.14	0.05	806	0.15	0.05
Q3	389	0.34	0.06	726	0.34	0.07	395	0.34	0.07	739	0.34	0.07
Q4	389	0.69	0.23	700	0.73	0.25	394	0.69	0.23	709	0.73	0.25

IHD=Ischemic Heart Disease

[a] Cumulative employment duration in taconite includes *any* work in taconite (i.e., not only individuals who worked in taconite, but those who worked in taconite at any time)

[b] Minimum and maximum values for quartiles of cumulative employment duration in taconite (in years) for IHD underlying [Q1=(0.003, 2.491); Q2=(2.500, 9.659); Q3=(9.670, 20.058); Q4=(20.071, 54.031)] and IHD underlying/contributing [Q1=(0.003, 2.418); Q2=(2.423, 9.637); Q3=(9.643, 20.049); Q4=(20.052, 54.031)]

[c] Only includes employment duration for production departments (i.e., concentrating, crushing, ore dressing, mining, & pelletizing)

[d] Minimum and maximum values for quartiles of cumulative employment duration in production departments (in years) for IHD underlying [Q1= (0.001, 0.975); Q2=(0.977, 3.436); Q3=(3.450, 12.016); Q4=(12.112, 45.240)] and IHD underlying/contributing [Q1= (0.003, 0.975); Q2=(0.977, 3.436); Q3=(3.450, 12.178); Q4=(12.200, 52.545)]

[e]Minimum and maximum values for quartiles of cumulative exposure to respirable dust (in mg/m^3*years) for IHD underlying [Q1=(0.001, 0.622); Q2=(0.623, 1.950); Q3=(1.952, 3.879); Q4=(3.879, 14.228)] and IHD underlying/contributing [Q1=(0.001, 0.618); Q2=(0.618, 1.949); Q3=(1.951, 3.881); Q4=(3.881, 14.228)]

[e]A total of 356 individuals (125 cases, 231 controls) were considered to have no cumulative respirable dust exposure because they were employed in hematite only

[g]Minimum and maximum values for quartiles of cumulative exposure to respirable silica (in mg/m^3*years) for IHD underlying [Q1=(0.000, 0.072); Q2=(0.072, 0.233); Q3=(0.233, 0.457); Q4=(0.457, 1.837)] and IHD underlying/contributing [Q1=(0.000, 0.071); Q2=(0.072, 0.232); Q3=(0.232, 0.458); Q4=(0.458, 1.837)]

Supplemental Table 4. Characteristics of and Exposures Among IHD Underlying/Contributing Cases[a] and Controls

	Cases			Controls		
	Mean	**SD**		**Mean**	**SD**	
Birthyear	1928	7.84		1928	7.67	
	N	**%**		**N**	**%**	
Sex						
F	36	1.69		71	1.72	
M	2,099	98.31		4,048	98.28	
Ore Type						
Hematite only	540	25.27		1,053	25.56	
Taconite only	777	36.39		1,567	38.04	
Taconite & Hematite	818	38.31		1,499	36.39	
Decade of Birth						
1920-1929	1,433	67.06		2,776	67.39	
1930-1939	497	23.28		965	23.43	
1940-1949	144	6.74		266	6.46	
1950-1960	61	2.86		112	2.72	
Employment Duration (in Years)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
By Industry[b]						
Taconite	1,595	11.86	10.04	3,066	12.25	10.45
Hematite	1,358	5.35	7.05	2,552	4.55	6.06
By Department						
Mining	828	6.82	8.13	1,384	6.51	8.01
Crushing	290	1.97	3.57	517	1.91	3.71
Concentrating	261	3.80	5.36	534	3.63	5.10
Pelletizing	415	2.61	5.08	714	3.70	6.63
Shop mobile	748	6.79	7.51	1,427	7.50	8.39
Shop stationary	336	5.80	7.36	713	6.62	7.96
Office/Control Room	131	7.88	8.00	333	7.97	7.93
Laborer	202	1.59	4.19	390	1.49	3.96
Ore Dressing	90	3.18	6.06	157	3.58	6.43
Unknown[c]	308	6.33	6.37	571	6.61	6.58
Respirable Exposures (in mg/m^3*years)						
Respirable Dust (RD)	1,595	2.55	2.29	3,066	2.61	2.40
Respirable Silica (RS)	1,578	0.30	0.28	3,031	0.30	0.29

[a]Cases are defined by IHD as an underlying cause of death *or* IHD as a contributing cause of death (with COPD as an underlying cause of death)
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive
[c]Unknown includes any individual who did not have a definitive job title or department (excludes laborer department)

Supplemental Table 5. Risk of IHD Mortality due to IHD Underlying & Contributing Causes of Death[a] by Cumulative Years of Employment and Cumulative Exposure

Cumulative Years of Employment	Hazards Ratio	95% CI
By Departments		
Concentrating	0.99	0.97, 1.02
Crushing	1.01	0.98, 1.05
Mining	1.01	1.00, 1.02
Office/Control Room	0.98	0.96, 1.00
Pelletizing	0.98	0.96, 1.00
Shop Mobile	0.99	0.98, 1.00
Shop Station	0.98	0.97, 1.00
Ore Dressing	1.00	0.97, 1.04
Laborer[b]	0.99	0.95, 1.03
Unknown[c]	0.99	0.97, 1.01
Hematite	1.02	1.01, 1.03
By Industry[d]		
Taconite	0.99	0.99, 1.00
Hematite	1.02	1.01, 1.03
By Production Departments		
Production	1.00	1.00, 1.01
Non-Production	0.99	0.98, 0.99
Laborer[b] & Unknown[c]	0.99	0.97, 1.00
Hematite	1.02	1.01, 1.03
Cumulative Exposure		
Respirable Dust (RD)	0.99	0.97, 1.02
Respirable Silica	1.02	0.84, 1.23

[a]Cases are defined by IHD as an underlying cause of death and IHD as a contributing cause of death (with COPD as an underlying cause of death)
[b]Includes any individual who did not have a definitive job title or department
[c]Includes laborers not assigned to a specific department in the mines
[d]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive

Supplemental Table 6. Risk of IHD Mortality Underlying/Contributing Causes of Death[a] by Quartiles in Separate Analyses of Employment Duration and Exposure

	Hazards Ratio	95% CI
Quartiles of Cumulative Years of Employment in Taconite		
Taconite Q1 (ref)		
Taconite Q2	0.93	0.78, 1.10
Taconite Q3	1.09	0.92, 1.30
Taconite Q4	0.90	0.75, 1.07
Hematite Only	0.97	0.82, 1.15
Quartiles of Cumulative Years of Employment in Production Departments		
Production Q1 (ref)		
Production Q2	1.16	0.94, 1.42
Production Q3	1.00	0.82, 1.23
Production Q4	1.10	0.89, 1.35
Non-Production	0.80	0.67, 0.97
Hematite Only	0.96	0.80, 1.16
Quartiles of Cumulative Respirable Dust Exposure		
RD Q1 (ref)		
RD Q2	1.00	0.84, 1.19
RD Q3	1.03	0.86, 1.22
RD Q4	0.98	0.83, 1.17
Hematite Only	1.00	0.85, 1.18
Quartiles of Cumulative Respirable Silica Exposure		
RS Q1 (ref)		
RS Q2	0.96	0.81, 1.14
RS Q3	1.06	0.89, 1.26
RS Q4	1.12	0.94, 1.33
Hematite Only	1.03	0.88, 1.22

[a]Cases are defined by IHD as an underlying cause of death and IHD as a contributing cause of death (with COPD as an underlying cause of death)

Supplemental Table 7. Selected Studies on Respirable Exposures and Ischemic Heart Disease Outcomes

First Author (Year)	Participants	Timeframe	Study Design	Outcome of Interest	Exposure of Interest	Exposure Summary Data	Exposure Assessment	Associations	Results
Rodins (2020)	4,814 participants	2000 to 2014	Prospective population-based study	CHD incidence	$PM_{2.5}$	Average for 2006-2008: Min=13.90 μg/m^3; Max=20.46 μg/ m^3 Average for 2001-2003: Min=15.36 μg/m^3; Max=22.10 μg/m^3	Residential area	Per IQR increase (i.e., 1.87 μg/m^3)	HR=0.89; 95%CI=0.75, 1.05
Ljungman (2019)	114,758 participants	1990 to 2011	Population-based multi-cohort study	IHD hospitalization or mortality (combined)	$PM_{2.5}$	Total exposure average=7.7ug/m^3	Residential area; mean exposure of the same year of the event, 1-5 years preceding the event, and 6-10 years preceding the event	Per IQR increase (i.e., 1.94 μg/m^3)	Results presented graphically; estimates for same year and 1-5 years were between 1.0 and 1.1 with 95%CIs that included the null value, the estimate for 6-10 years was between 0.9 and 1.0 with 95%CIs that included the null
Thurston (2016)	445,860 participants	1982 to 2004	Prospective population-based study	IHD mortality	$PM_{2.5}$	Range of mean concentrations (2000-2005): 8.6-26.9 μg/m^3	Residential area	Per IQR increase (i.e., 3.145 μg/m^3)	HR=1.03; 95%CI=1.00, 1.06
Costello (2015)	39,412 autoworkers	3 years after hire date to death or 1994	Cohort study	IHD mortality	$PM_{3.5}$ from straight metalworking fluid (mg/m^3)	Range of annual mean $PM_{3.5}$ from straight metalworking fluid (mg/m^3) (1920-1994) (based on graphical representation): approximately 0.0 mg/m^3 to 0.85 mg/m^3	Modeled estimates based on personal and area samples for particulate matter (mg/m^3)	Exposure quintiles compared to unexposed	1941 to 1994 (highest exposure quantile (>2.77 mg/m^3) v. unexposed): HR=1.53; 95%CI=1.15, 2.05 1941 to 1970 (highest exposure quantile (>1.66 mg/m^3) v. unexposed): HR=1.07; 95%CI=0.68, 1.69 1971 to 1994 (highest exposure quantile (>3.40 mg/m^3) v. unexposed): HR=1.64; 95%CI=1.12, 2.41

Neophytou (2016)	6,579 smelters 7,432 fabricators	1998 to 2003	Cohort study	First occurrence of IHD (mortality or incidence)	$PM_{2.5}$	Mean annual PM2.5 (smelters): 1.98 (SD=1.62) mg/m^3 Mean annual PM2.5 (fabricators): 0.34 (SD=0.50) mg/m^3	Modeled estimates based on 8000 personal samples collected over 25 years	Above the 10th percentile of $PM_{2.5}$ v. below the 10th percentile of $PM_{2.5}$	**Traditional Cox Models** Fabricators: HR=1.24; 95%CI=0.92, 1.68 Smelters (approximated from Figure 2): HR=1.6; 95%CI=1.1, 2.5 **Cox Marginal Structural Models** Fabricators: HR=1.34; 95%CI=0.98, 1.83 Smelters: HR=1.98; 95%CI=1.18, 3.32
Lai (2018)	7,665 Chinese iron miners	1960 to 2012	Cohort study	IHD mortality	Respirable silica	Average annual respirable silica concentration (mg/m^3): 0.04 (SD=0.04) mg/m^3	Modeled exposure based on historical measurements using a JEM	Increase of 1 mg/m^3*year in cumulative respirable silica	HR=1.134; 95%CI=0.990, 1.298
								Quartiles of exposure v. unexposed	Low (0.4935 mg/m^3*y or below): HR=1.190; 95%CI=0.738, 1.918 medium (0.4935 to 0.8423 mg/m^3*y): HR=1.538;95%CI=1.063, 2.226 high (0.8423 mg/m^3*y or above): HR=1.781; 95%CI=1.281, 2.476
Wang (2020)	44,708 male metal mine and pottery workers	1950 to 2003	Cohort study	IHD mortality	Respirable silica	Average cumulative silica dust exposure: 3.64 (SD=4.17) mg/m^3	Estimated silica exposure based silica content in total dust and used a JEM to estimate exposures for each workers	Quartiles of exposure v. never exposed	low (0 to 1.056 mg/m^3*years): HR=1.20; 95%CI=0.94, 1.55 medium (1.057 to 3.925 mg/m^3*years): HR=1.21; 95%CI=0.95, 1.54 high (>3.925 mg/m^3*years): HR=0.77; 95%CI=0.58, 1.01

CHD=Coronary Heart Disease

Supplemental Table 8. Cumulative Employment Duration (in years) by Production Departments

	COPD Underlying						COPD Underlying/Contributing					
	Cases			Controls			Cases			Controls		
By Production Departments	**N**	**Mean (yrs)**	**SD**	**N**	**Mean (yrs)**	**SD**	**N**	**Mean (yrs)**	**SD**	**N**	**Mean (yrs)**	**SD**
Production	167	7.0	8.7	311	6.8	8.7	241	6.8	7.8	446	6.9	8.2
Non-production	153	7.9	9.1	322	9.9	9.6	216	7.9	8.7	452	9.6	9.4
Hematite[a]	219	5.6	8.1	434	4.4	6.1	314	5.8	7.7	611	5.0	6.5
Unknown[b]	59	9.0	7.9	83	6.7	6.5	90	7.3	7.0	148	7.7	7.2

COPD=Chronic Obstructive Pulmonary Disease

[a]Hematite includes any individual who worked within hematite (i.e., it is not mutually exclusive to the other departments)

[b]Unknown includes any individual who did not have a definitive job title or department (excludes laborer department)

Supplemental Table 9. Quartiles of Cumulative Employment Duration (in years) by Employment in the Taconite Industry and the Production Department and Exposure to Respirable Dust and Respirable Silica, Respectively (in mg/m³*years)

	COPD Underlying						COPD Underlying/Contributing					
	Cases			Controls			Cases			Controls		
Cumulative Employment Duration in Taconite[a,b]	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Q1	66	0.90	0.63	124	0.90	0.64	90	1.00	0.68	168	0.95	0.68
Q2	66	4.54	1.66	119	4.49	1.79	89	4.85	1.82	170	5.06	2.05
Q3	66	13.95	3.55	119	13.96	3.78	90	14.56	3.42	157	14.87	3.31
Q4	65	26.71	3.63	134	27.06	4.00	89	27.17	3.44	202	27.36	4.12
Cumulative Employment Duration in Production[d,e]												
Q1	42	0.41	0.29	85	0.35	0.27	61	0.56	0.40	128	0.48	0.35
Q2	42	1.95	0.82	90	1.97	0.76	60	2.33	0.78	106	2.22	0.75
Q3	42	5.67	1.62	58	5.72	1.44	60	6.08	1.61	94	6.23	1.63
Q4	41	20.47	7.02	78	20.03	7.01	60	18.45	6.77	118	18.70	6.79
Cumulative Exposure to Respirable Dust[e]												
Q1	66	0.22	0.12	106	0.20	0.11	90	0.25	0.14	161	0.24	0.15
Q2	66	0.97	0.36	136	0.87	0.34	89	1.11	0.52	175	1.04	0.38
Q3	66	2.51	0.53	110	2.58	0.53	90	2.80	1.83	166	2.92	0.60
Q4	65	5.75	1.86	144	5.84	2.03	89	6.04	3.97	195	6.27	1.91
Cumulative Exposure to Respirable Silica												
Q1	71	0.02	0.01	115	0.02	0.01	95	0.03	0.02	168	0.03	0.02
Q2	64	0.11	0.04	126	0.11	0.04	87	0.12	0.04	166	0.12	0.06
Q3	64	0.28	0.07	113	0.29	0.07	88	0.31	0.07	171	0.31	0.07
Q4	64	0.68	0.26	142	0.69	0.28	88	0.71	0.24	192	0.73	0.27

COPD=Chronic Obstructive Pulmonary Disease

[a] Cumulative employment duration in taconite includes *any* work in taconite (i.e., not only individuals who worked in taconite, but those who worked in taconite at any time)

[b] Minimum and maximum values for quartiles of cumulative employment duration in taconite (in years) for COPD underlying [Q1=(0.002, 2.086); Q2=(2.103, 7.836); Q3=(7.866, 21.084); Q4=(21.123, 47.039)] and COPD underlying/contributing [Q1=(0.003, 2.311); Q2=(2.313, 8.956); Q3=(8.958, 21.320); Q4=(21.328, 52.572)]

[d] Only includes employment duration for production departments (i.e., concentrating, crushing, ore dressing, mining, & pelletizing)

[e] Minimum and maximum values for quartiles of cumulative employment duration in production departments (in years) for COPD underlying [Q1= (0.003, 0.917); Q2=(0.964, 3.619); Q3=(3.671, 8.906); Q4=(9.150, 37.895)] and COPD underlying/contributing [Q1= (0.003, 1.218); Q2=(1.236, 3.874); Q3=(3.875, 9.450); Q4=(9.515, 37.895)]

[e]Minimum and maximum values for quartiles of cumulative exposure to respirable dust (in mg/m^3*years) for COPD underlying [Q1= (0.004, 0.412); Q2=(0.412, 1.608); Q3=(1.616, 3.522); Q4=(3.533, 14.531)] and COPD underlying/contributing [Q1=(0.004, 0.511); Q2=(0.519, 1.825); Q3=(1.833, 3.959); Q4=(3.965, 12.466)]

[e]For COPD underlying a total of 259 individuals (86 cases, 173 controls) and for COPD underlying/contributing a total of 356 individuals (125 cases, 231 controls) were considered to have no cumulative respirable dust exposure because they were employed in hematite only

[g]Minimum and maximum values for quartiles of cumulative exposure to respirable silica (in mg/m^3*years) for COPD underlying [Q1=(0.000, 0.0.49); Q2=(0.049, 0.185); Q3=(0.185, 0.410); Q4=(0.412, 1.705)] and COPD underlying/contributing [Q1=(0.000, 0.056); Q2=(0.057, 0.195); Q3=(0.195, 0.463); Q4=(0.437, 1.737)]

Supplemental Table 10. Characteristics of and Exposures Among COPD Cases[a] and Controls (Underlying and Contributing Causes of Death)

	Cases			Controls		
	Mean	**SD**		**Mean**	**SD**	
Birthyear	1927	6.2		1927	6.0	
	N	**%**		**N**	**%**	
Sex						
F	20	4.1		37	4.0	
M	463	95.9		891	96.0	
Ore Type						
Hematite only	125	25.9		231	24.9	
Taconite only	169	35.0		317	34.2	
Taconite & Hematite	189	39.1		380	40.9	
Decade of Birth						
1920-1929	342	70.8		653	70.4	
1930-1939	114	23.6		229	24.7	
1940-1949	24	5.0		40	4.3	
1950-1960	3	0.6		6	0.6	
Employment Duration (in Years)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
By Industry[b]						
Taconite	358	11.9	10.4	697	12.74	10.9
Hematite	314	5.8	7.7	611	4.96	6.5
By Department						
Mining	174	6.3	7.8	317	5.96	7.5
Crushing	57	2.1	3.3	110	2.12	3.2
Concentrating	57	2.8	3.9	110	3.11	4.8
Pelletizing	87	3.0	5.1	142	3.72	6.2
Shop mobile	151	6.9	7.7	327	8.28	8.7
Shop stationary	68	4.5	5.6	143	6.18	7.7
Office/Control Room	45	8.1	9.1	78	9.40	9.4
Laborer	83	2.9	4.9	95	3.39	5.7
Ore Dressing	6	1.3	1.9	25	3.79	6.6
Unknown[c]	90	7.3	7.0	148	7.73	7.2
Respirable Exposures (in mg/m^3*years)						
Respirable Dust (RD)	358	2.54	2.39	697	2.76	2.61
Respirable Silica	358	0.29	0.29	697	0.31	0.32

[a]Cases are defined by COPD as an underlying cause of death *or* COPD as a contributing cause of death (with IHD as an underlying cause of death)
[b]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive
[c]Unknown includes any individual who did not have a definitive job title or department (excludes laborer department)

Supplemental Table 11. Risk of COPD Mortality due to Underlying & Contributing Causes of Death[a] by Cumulative Years of Employment and Cumulative Exposure

Cumulative Years of Employment	Hazards Ratio	95% CI
By Departments		
Concentrating	0.99	0.93, 1.06
Crushing	0.98	0.90, 1.07
Mining	1.00	0.98, 1.03
Office/Control Room	1.00	0.97, 1.03
Pelletizing	0.99	0.95, 1.03
Shop Mobile	0.98	0.96, 1.00
Shop Station	0.97	0.93, 1.01
Ore Dressing	0.79	0.55, 1.15
Laborer[b]	1.03	0.97, 1.08
Unknown[c]	1.00	0.97, 1.03
Hematite	1.02	1.00, 1.04
By Industry[d]		
Taconite	0.99	0.98, 1.00
Hematite	1.02	1.00, 1.04
By Production Departments		
Production	1.00	0.98, 1.02
Non-Production	0.98	0.96, 0.99
Laborer[b] & Unknown[c]	1.01	0.98, 1.03
Hematite	1.02	1.00, 1.03
Cumulative Exposure		
Respirable Dust (RD)	0.96	0.92, 1.01
Respirable Silica	0.77	0.52, 1.14

[a]Cases are defined by COPD as an underlying cause of death and COPD as a contributing cause of death (with IHD as an underlying cause of death)

[b]Includes any individual who did not have a definitive job title or department

[c]Includes laborers not assigned to a specific department in the mines

[d]Taconite represents any work in taconite & hematite represents any work in hematite; the two are not mutually exclusive

Supplemental Table 12. Risk of COPD Mortality Contributing Causes of Death[a] by Quartiles in Separate Analyses of Employment Duration and Exposure

	Hazards Ratio	95% CI
Quartiles of Cumulative Years of Employment in Taconite		
Taconite Q1 (ref)		
Taconite Q2	1.01	0.70, 1.45
Taconite Q3	1.10	0.77, 1.58
Taconite Q4	0.86	0.59, 1.24
Hematite Only	1.07	0.75, 1.52
Quartiles of Cumulative Years of Employment in Production Departments		
Production Q1 (ref)		
Production Q2	1.21	0.78, 1.87
Production Q3	1.40	0.89, 2.20
Production Q4	1.10	0.70, 1.72
Non-Production	1.00	0.68, 1.46
Hematite Only	1.20	0.81, 1.78
Quartiles of Cumulative Respirable Dust Exposure		
RD Q1 (ref)		
RD Q2	0.96	0.67, 1.38
RD Q3	1.00	0.70, 1.44
RD Q4	0.85	0.58, 1.23
Hematite Only	1.02	0.72, 1.46
Quartiles of Cumulative Respirable Silica Exposure		
RS Q1 (ref)		
RS Q2	0.95	0.66, 1.37
RS Q3	0.94	0.66, 1.35
RS Q4	0.82	0.56, 1.20
Hematite Only	1.00	0.71, 1.42

[a]Cases are defined by COPD as an underlying cause of death *or* COPD as a contributing cause of death (with IHD as an underlying cause of death)

Supplemental Table 13. Selected Studies on Respirable Exposures and COPD

First Author	Participants	Timeframe	Study Design	Outcome of Interest	Exposure of Interest	Exposure Summary Data	Exposure Assessment	Associations	Results
Bakke (1991)	714 participants	1985, 1987-1988	Population-based cross-sectional survey	Chronic Obstructive Lung Disease	General, unspecified "airborne exposure"	For present job moderate airborne exposure (AE+): 26% high airborne exposure (AE++): 3%	Collected via survey, authors assigned no airborne exposure (AE-), moderate airborne exposure (AE+), and high airborne exposure (AE++)	Moderate or High airborne exposure v. no airborne exposure	AE+: OR=1.4; 95%CI=0.9, 3.0 AE++: OR=3.6; 95%CI=1.3, 9.9
Weinmann (2008)	388 cases and 356 controls	2000 to 2002	Population-based case control study	COPD diagnosis	Any dust, gas, vapor, sensitizer, organic solvent or diesel exhaust	Not Reported	Industrial hygienists evaluated likelihood of exposure including to any dust, gas, vapor, sensitizer, organic solvent or diesel exhaust to create a JEM	Exposure to any dust, irritant gases or vapors, sensitizers, organic solvents, or diesel exhaust v. never exposed	OR=1.5; 95%CI=1.1, 2.1
Blanc (2009)	1,202 cases and 302 controls		Population-based case control study	COPD diagnosis	Vapors, gas, dust, or fumes	Exposure probability among cases based on JEM: Low: 467 (67%) Intermediate: 70 (9%) High: 177 (24%)	Occupational risk assessed using a JEM based on job title data collected via interview	Intermediate and High exposure probability v. Low exposure probability	Low (ref) Intermediate: OR=1.27; 95%CI=0.74, 2.19 High: OR=2.27; 95%CI=1.46, 3.52

Miller (2010)	17,820 male British colliery workers	1959 to 2006	Mortality study	COPD mortality	Respirable dust and quartz	Averages of cumulative respirable dust among 5 surveys ranged from 131.4 to 154.4 g.h.m-3 Averages of cumulative respirable quartz among 5 surveys ranged from 6.24 to 7.01 g.h.m-3	Modeled estimates based on sampling and applied to job titles	Respirable dust: per 100 g.h.m-3 increase Respirable quartz: per 5 g.h.m-3 increase	**Respirable dust** No lag: HR=1.14; 95%CI=1.08, 1.20 15-year lag: HR=1.17; 95%CI=1.11, 1.24 **Respirable quartz** No lag: HR=1.08; 95%CI=1.03, 1.13 15-year lag: HR=1.11; 95%CI=1.05, 1.16 **Lagged exposure for dust and quartz** Respirable dust: HR=1.21; 95%CI=1.11, 1.32 Respirable silica: HR=0.96; 95%CI=0.88, 1.04
Lenander-Ramirez (2022)	1,752 Swedish foundry workers	2001 to 2017	Incidence study	COPD incidence	Respirable dust and silica	Average Cumulative Respirable dust: 10.1 mg/m^3*year Average Cumulative Respirable silica: 0.40 mg/m^3*year	Standardized to the general Swedish population	Comparison to the general Swedish population	**Respirable dust** ≤2.76 mg/m^3*years: SIR= 1.81; 95%CI=1.25, 2.54 2.77-9.82 mg/m^3*years: SIR=2.04; 95%CI=1.42, 2.83 9.83+ mg/m^3*years: SIR=1.97; 95%CI=1.36, 2.77 **Respirable silica** ≤0.14 mg/m^3*years: SIR=2.35; 95%CI=1.56, 3.40 0.15-0.38 mg/m^3*years: SIR=2.07; 95%CI=1.43, 2.91 0.39+ mg/m^3*years: SIR=1.64; 95%CI=1.17, 2.24